

Olefin Metathesis — Application in the Synthesis of Natural Products and Related Organic Compounds

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Exchange of an alkene unit of an olefinic compound with alkene unit of another compound (metathesis) leads to a new olefinic compound. This process takes place in presence of a transition metal alkylidene complex as catalyst. A variety of synthetic operations such as ring closing metathesis, ring opening metathesis, cross metathesis, enyne metathesis and domino processes involving ring opening-ring closing and cross metathesis can be achieved to construct novel molecular architectures that are difficult to make by other reactions. This account presents briefly the contributions mainly from authors' laboratory on applications of the various metathetic processes for synthesis of natural products and related molecules.

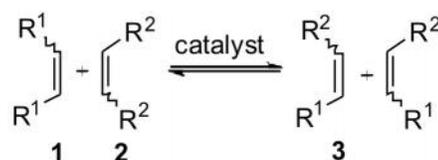
Key Words: Olefin Metathesis; Diels-Alder Reaction; Domino Process; Ring Closure Reaction; Terpenes; Carbasugars

1. Introduction

The importance of natural products as valuable sources of medicines has been well recognized. A large number of biologically active natural products possess densely functionalised complex molecular structures containing multiple rings of different sizes. Thus synthesis of natural products and related molecules with complete regio- and stereocontrol renders ring construction a fundamental process in synthetic organic chemistry. Most direct method for ring construction involves cyclization of acyclic precursors through cationic (Godoi *et al.* 1990), anionic (Godoi *et al.* 1990; Murphy and Wattanasin 1983) and radical mediated (Majumdar *et al.* 2012) processes. Common rings such as 5-7 membered ones are easily available by these cyclization processes. However, synthesis of medium (Kleinke *et al.* 2012) or large rings by classical cyclisation methods either proceeds with low yields or does not proceed at all due to unfavourable enthalpic and entropic factors. Olefin metathesis (Kotha and Dipak 2012) has

emerged as a powerful tool for carbon-carbon bond formation enabling synthesis of rings of different sizes from common rings to medium rings and even macrocycles under mild reaction condition.

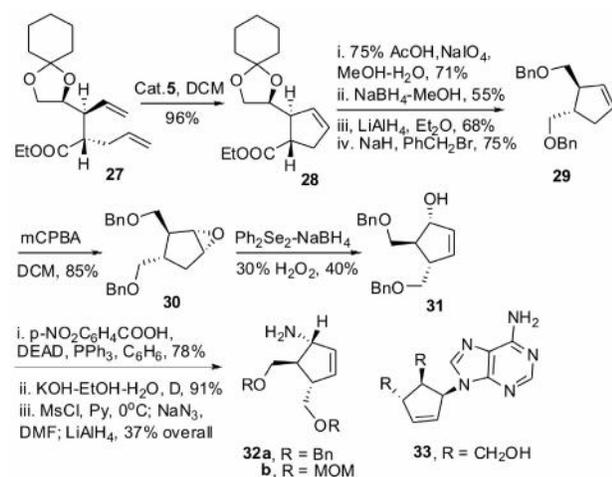
Olefin metathesis is defined as a process in which alkylidene units between two substituted alkenes **1** and **2** undergoes mutual exchange in the presence of a transition metal carbene complex as catalyst to produce a new olefin **3** (Scheme 1). As proposed by Herisson and Chauvin (1971) metathesis proceeds through [2+2] cycloaddition between an alkene and a metal carbene complex to produce a metallacyclobutane **4**.



Scheme 1

y j gp'tgcvgf'y kj 'vj g'uco g'ecvncf uv'wvpgt'kf gpvkcnc
 eqpf kxkp'vq'r tqf weg **22'lp'**; 5' '{kgrf 0Uko krcn'f. 'vj g
 f kpgqm**20b'**cpf **20c'**y kj 'ukn' m'z { 'b gy { n'c'p'f 'cegqz {
 o gy { n'i tqw 't'gur gev'xgn'f 'c'v'vj g'cm'f' r'e'ctdqp'y cu
 h'wv'p'f 'vq'r tqeggf 'c'v'c' b' wej 'h'v'ug'f 't'c'v'g'v'q'r tqf weg'vj g
 e { emr gpv'p'g'f g'k'x'c'v'x'g'u **21b'**cpf **21c'**lp'; 5' "cpf
 ; 3' '{kgrf u't'gur gev'xgn'f 0Vj g'k'p'g't'v'p'g'u'q'h'vj g'f kpgqm
20a' v'q'y c't'f u' TEO "ku" r' quukdn'f "f w'g" v'q" ut'q'p'i
 eqo r' r'g'z'c'v'k'p'q'h'QJ 'i tqw 'v'q' T'w'y j' k'ej 't'g'c't'f u' TEO 0
 Eqp'ugs w'p'v'w'f "r' t'q'v'g'v'k'p'q'h'QJ 'i tqw 'f' k'o k'p'k'ij' gu
 e'j g'r'v'k'p'k'p'v'j g'f k'p'g'u'c'p'f 'r' t'q'o q'v'g'u' TEO 0f' q'y g'x'g't'
 e'g't'c'k'p'co q'w'p'v'q'h'ej g'r'v'k'p'q'h' T'w'd { "vj g'c'm'q'z {
 q'z { i' g'p'q'h'vj g'f k'p'g'u'c'u'uj' q'y p'k'p'v'j g'ut'w'w'g't' **24**
 u'g'g'o u'v'q' d'g' d'g'p'g'h'k'c'n' *P c { g'm'g'v'c'n' 04228-0K' o c {
 f' k't'g'v'o g'v'c'y g'u'k'u' k'p'k'c'v'k'p'c'v'vj g'c'm'g'p'g'p'g'c't'g'u'v'v'q
 v'j g'c'm'q'z { 'i tqw 'c'p'f 'vj w'u'q'x'g't't'k'f' g'u'v'j g'eqo r' g'v'k'x'g'
 p'q'p'o g'v'c'y g'v'e' h't'c'i o g'p'v'k'p'p' r' t'q'g'u'f' w'g'v'q'c'm'f' r'e
 u'g'eq'p'f c't { "QJ 'i tqw 0Vj g'd'w'm'k'g't'c'm'q'z { "i tqw u'lp
 v'j g'f k'p'g'm'c'm'q' h'c'k'k'c'v'g'f' k'u'q'k'c'v'k'p'q'h'vj g'q'z { i' g'p
 c'v'q'o 'h't'q'o 'vj g'v'c'd'k'k'f' g'f 'T'w'c't'd'g'p'g' **24'** t'g's w't'g'f' h'q't
 u'w'd'g's w'p'v't'g'c'v'k'p'y kj 'vj g'v'g'eq'p'f 'c'm'g'p'g'w'p'k'0Vj w'u
 c'g'v'c'v'g' d'g'k'p'i c'c' d'g'w'g't' r'g'c'x'k'p'i "i tqw 'v'j c'p' u'k'n'f' m'z { .
 f' k'u'q'k'c'v'g'f 'c'v'c' h'v'ug'f 't'c'v'g' h't'q'o 'vj g'v'c'd'k'k'f' g'f 'eqo r' r'g'z
24' c'p'f 'vj g't'k'p'i 'em'q'w't'g'y' c'u'eqo r' r'g'v'k'p'q'p'n'f' 4' 0Vj g
 t'q'g'q'h'c'm'q'z { "i tqw u'lp' h'c'k'k'c'v'k'p'i TEO 'eq'w'f' d'g
 w'p'f' g't'u'q'q'f' h't'q'o TEO 'q'h'vj g'f k'p'g'm' **25'** r'c'v'k'p'i 'c'p {
 c'm'q'z { "o gy { n'i tqw "r'g'c'f' k'p'i "v'q" c"o k'z'w't'g'q'h'vj g
 u'v'c't'v'k'p'i 'f' k'p'g' **25'** c'p'f 'vj g' TEO 'r' t'q'f' w'v'v' **26'** k'p'9-5' t'c'v'k'
 w'p'f' g't'k'f' g'p'v'k'c'n't'g'c'v'k'p'eq'p'f' k'k'p'0

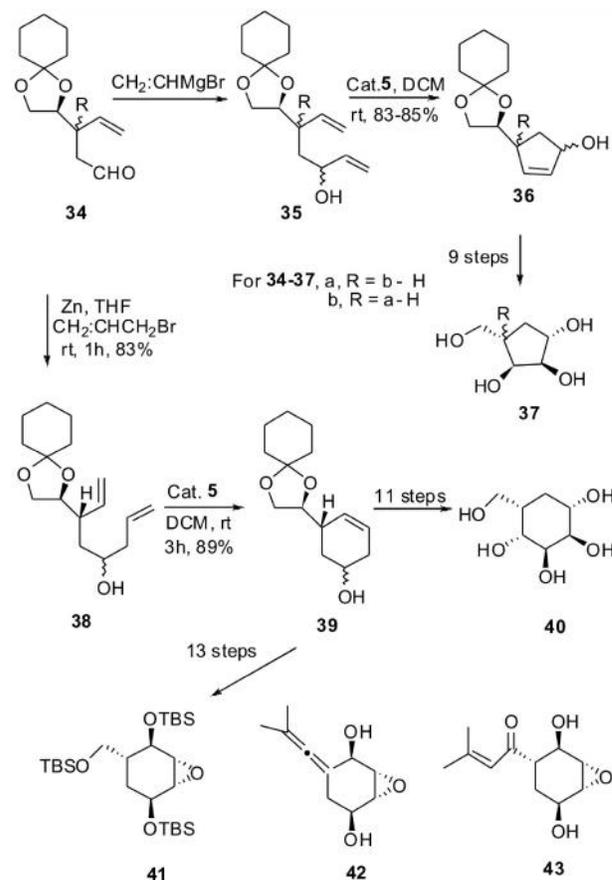
TEO 'y' c'u'w'ug'f' 'c'u'c' h'g'f' 'u'v'g'r' 'k'p'v'j' g'u' p'v'j' g'u'k'u'q'h
 v'j g'p'w'v'g'q'k'f' g'DEC' "D'c'p'g't' l'g'g'v'c'n' 04227-0Vt'g'c'v'o g'p'v'



Scheme 9

q'h'vj g'f k'p'g' **27'** y kj 'vj g'ecvncf uv'5' h'g'f' 'v'q' u'o q'q'y 't'k'p'i
 em'q'w't'g'v'q' h'q't'o 'vj g'v'c' { emr gpv'p'g'f' g'k'x'c'v'x'g' **28'** k'p'; 8'
 { k'grf 0Vj g'v'c' { emr gpv'p'g'y' c'u'v'j g'p'v't'c'p'uh't'o g'f 'v'q'v'j g
 e { emr gpv'p'g'f' n'c'o k'p'g' **32a'** c'u'v'j' q'y p'k'p'U'ej' g'o g'; 0Vj g
 O QO "g'y g't'c'p'c'm'i w'g' **32b'** k'u" v'j g' r' t'g'w'w'q't' "q'h'vj g
 p'w'v'g'q'k'f' g'DEC **330**

Eqo r' q'w'p'f' u'eq'p'v'k'p'k'p'i 'e'c't'd'c'u'w'i c't' b' q'k'g'v'k'u'c't'g'
 r' q'v'g'p'v'k'c'n'v'j g't'c'r' g'w'k'e'c'i' g'p'u'0C'p'w'o d'g't' q'h'è'c't'd'c'u'w'i c't/
 eq'p'v'k'p'k'p'i 'p'w'v'g'q'k'f' g'c'p'c'm'i' w'g'u'g'z'j' k'd'k'u'r' t'q'o k'k'p'i
 c'p'v'k'x'k'c'n' c'v'k'x'k'k'g'u'0'Q'n'k'i q'u'c'ee'j' c't'k'f' g" c'p'c'm'i' w'g'u
 eq'p'v'k'p'k'p'i 'e'c't'd'c'u'w'i c't' t'g'u'k'f' w'g'u'j' c'x'g' d'g'g'p' t'g'r' q't'w'f'
 v'q' d'g'g'h'k'k'p'v'i n'f' e'q'u' { n't'c'p'uh't'g'c'ug' k'p'j' k'd'k'q't'u' y' j' k'ej
 j' c'x'g' eq'p'k'f' g't'c'd'g' "v'j g't'c'r' g'w'k'e" r' q'v'g'p'v'k'c'n' k'p'v'j g
 o c'p'c'i' g'o g'p'v'q'h'è'c'p'eg't' f' k'c'd'g'v'u' c'p'f' 'x'k'c'n'k'p'h'g'v'k'p'u'0
 Vj w'u'f' g'x'g'm'r' o g'p'v'q'h'p'g'y' "c'r' r' t'q'c'ej' g'u' h'q't' "u' { p'v'j' g'u'k'u
 q'h'è'c't'd'c'u'w'i c't'u' k'u'c'p'k'o r' q't'w'p'v'c't'g' k'p'è'q'p'v'g'o r' q't'c't' {
 q't'i' c'p'k'e' "u' { p'v'j' g'u'k'u'0' E'c't'd'c'u'w'i c't' "u' { p'v'j' g'u'k'u' r' q'u'g'u' i' t'g'c'v'
 e'j' c'm'g'p'i' g' "k'p' "v'g't'o u' "q'h' "v'g't' g'q'u'g'v'g'v'k'g' "k'p'v'q'f' w'v'k'p'p'
 q'h' "o w'v'k'r' g' "j' { f' t'q'z { n' "i' tqw u'0' "k'p' "q'w' "c'r' r' t'q'c'ej'



Scheme 10

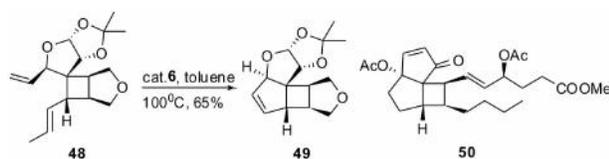
*I j quj gv'c'04228+'vq'ectdcuwi ctu. TEO 'r m{gf 'vj g ng{ "tqng" *Uej go g'32+0'Vj g'wpks wg' hccwtg' qh' qwt cr r tqcej 'ku' gcu{ "ceeguuklrk' qh' dqvj B/F/ "cpf B/N/ ectdctkdqhtcpqug0Vj g'f kpgg 35a' r tgr ctgf 'htqo 'vj g crf gj {f g 34a' qp' o gvcj guku' y kj "vj g' ecvñ{ uv 5 r tqxf gf "vj g' e{ emj gpvqpqn 36a' kp' gzegm'pv' { kgrf 0 Vj g' kp' vgt pcn' cmgpg' w'pkv' y cu' vj gp' g'zr n'kxgf "vq kp' vqf weg' j {f tqz { n' i tqw u' d { "eku' f kj {f tqz { r'v'k'p' y kj 'QuQ₆ U'gtgq/ ugrge'v'k'k' f' w'k'p' i' k'j {f tqz { r'v'k'p' y cu' eq'p'v'q' m'ef' d' { 'vj g' d'w'm'q'h'v'j g' h'g'v'c'n' l'w' d' u'k' w'g'p' 0' k'p' vj ku' y c' . B/N/ ectdctkdqhtcpqug 37a' ecn' dg u{ pvj guku' gf 0 Hq' m'q' y k'p' i' " vj ku' r tqv'eqn B/F/ ectdctkdqhtcpqug 37b' y cu' u{ pvj guku' gf 'vj tqw' j TEO qh' vj g' f kpgg 35b' r tgr ctgf 'htqo vj g' crf gj {f g 34b' 0 Uko k'c'tn' f' k'p' qn 38. r tgr ctgf 'htqo 34a. 'qp' t'g'c'v' o gpv y kj "vj g' ecvñ{ uv 5" i c'x'g' vj g' e{ emj g'z'g'p'q'n 39' 0 Vj g' e{ emj g'z'g'p'q'n 39' y cu' vj gp' v'c'p' u' h'q'to gf 'vq' e'c't'd'c' B/N/ i w'q'r { t'c'p'q'u'g 40' 0 Vj g' e{ emj g'z'g'p'q'n 39' y cu' c'n'q go r m'q' {gf "]35_ 'cu' cp' kp' vgt'o gf k'c'v'g' h'q't' vj g' u{ pvj guku' qh' 4.5/ gr qz { /u' p/ 3.6/ e{ emj g'z'c'p'g' f' k'q'n'f' g't'k'c'v'k'g 41. ut vew'c'no q'v'k'h' r t'g'g'p'v' k'p' c' r'c'ti g' p'w'o d'g't' q'h' j k' j n' d'k'q'm' i k'c'm' { 'c'v'k'g' r' q'n' n'g'v'k'f' g' p'c'w't'c'n'r' t'q'f' w'ew' u'w'ej cu' g'w'w' { r'z'k'f' g' C 42. g'w'w' { r'z'k'f' g' D 43' g'w'e' 0

Kp' vj g' h'k' u'v' q'v'c'n' u{ pvj guku' *O c'k' { "c'p'f' "I j quj 4229+'q'h'v'j g' p'q'r'k'i p'c'p' u'g's w'q'u'g'o r g't'x'k'p' C 47. TEO y cu' w'ug'f' v'q' e'q'p'v't' w'ew' vj g' u' r' k'q']60' _'f' g' e'c'p'g' u{ u'v'g'o r t'g'g'p'v' k'p' k'v' *Uej go g'33+0

Vj g' f kpgg 45' r tgr ctgf 'htqo 'vj g' e{ emj g'z'c'p'q'p'g f g't'k'c'v'k'g 44' qp' t'g'c'v' o gpv' y kj "vj g' ecvñ{ uv 5' c'v' t'v r tqxf gf "vj g' e{ emj gpvqpqn' f g't'k'c'v'k'g 46' 0 Vj g' eqo r q'w'p'f 46' y cu' vj gp' v'c'p' u' h'q'to gf " vq u'g's w'q'u'g'o r g't'x'k'p' 47' 0



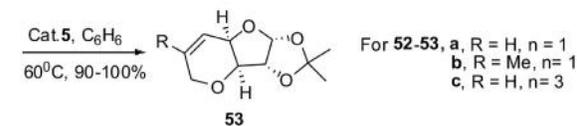
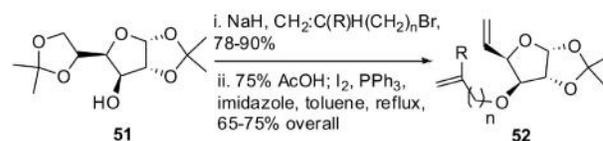
Scheme 11



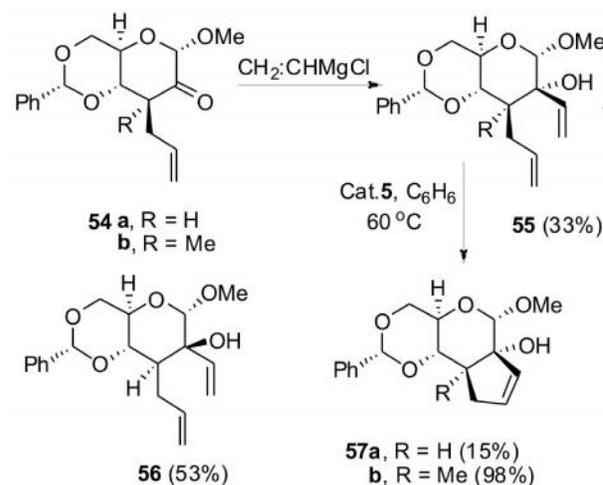
Scheme 12

TEO "qh' c' f kpgg' go d'q'f' k'g'f' "kp' vj g' j k' j n' f' u'g't'k'c'm' { 'e'q'p'i' g'w'g'f' 'v't'k' { 'e'k'k' u' { u'v'g'o 48' j' cu' d'g'g'p' w'ug'f]37_ 'cu' c' n'g' { 'u'v'g'r' "kp' vj g' u' { pvj guku' qh' vj g' v'g't'c'e { 'e'rg 49. 'c' t' t'q' l'g' e'v'g'f' kp' vgt'o gf k'c'v'g' v'q'y c't'f' u' vj g' u' { pvj guku' qh' c'p' w'p'w'w'c'n' o c't'k'p'g' r' t'q'u'c'p'q'k'f' v't'k' { 'e'q'v'c'w'w'q'p'g 50 *Uej go g'34+0

Q'p'g' q'h' vj g' y k'f' g'n' { 'g'o r m'q' { gf 'c'r r tqcej g'u' h'q't' vj g' u' { pvj guku' qh' g'p'c'p'v'k'q'o g't'k'c'm' { 'r' w't'g' v'c'ti' g'u' l'p'x'q'r'k'g'u' c'p'p'w'r'v'k'p' q'h' e'c't'd'q'e { 'e'k'k' u' y g'n' c' u' j' g'v'g't'q'e { 'e'k'k' u' t'k'p'i' u' qh' x'c't'k'q'u' u'k' g'u' q'p' v'q' e'c't'd'q'j {f t'c'v'g'u' 0' j' q'y g'x'g't. e'c't'd'q'j {f t'c'v'g'u' c't'g' u'w'ue'g'r' v'k'd'g' v'q' t'g'c'v'k'p' e'q'p'f' k'k'q'p'u' vj c'v'c't'g' e'q'o o q'p'n' { 'w'ug'f' h'q't' t'k'p'i' c'p'p'w'r'v'k'p' 0' Q'g'h'k'p' o g'v'c'j' guku' j' cu' r' tqxf gf "c' w'p'k' s'g' c'r r tqcej 'h'q't' t'k'p'i' c'p'p'w'r'v'k'p' q'p' v'q' e'c't'd'q'j {f t'c'v'g'u' 0' H'k'x'g' v'q' p'k'p'g/ o go d'g't'g'f' t'k'p'i' u' e'c'p' d'g' c'p'p'w'r'v'g'f' q'p' v'q' c'r r t'q'r' t'k'c'v'g' u'w'i' c't' f' g't'k'c'v'k'g' u' 0' H'q't' g'z'c'o r' g'g. TEO "qh' vj g' f kpgg 52a' r tgr ctgf 'htqo 'f' k'c'g'v'q'p'g' i' n'w'eq'ug 51' q'p' j' g'c'v'k'p'i' k'p' d'g'p'l' g'p'g' c'v' 82°C with Grubbs' catalyst 5' n'g'f' v'q



Scheme 13

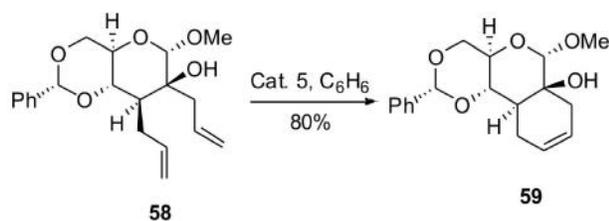


Scheme 14

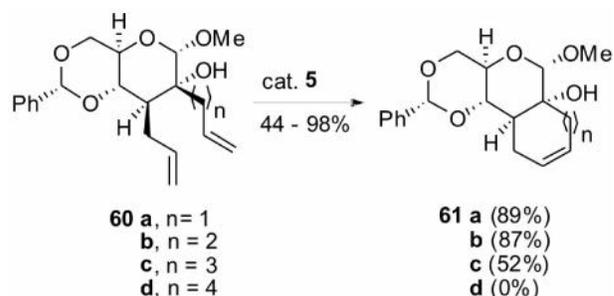
hcekg'cppwrcvqp'qhf kj { f tqr { tcp'tkpi 'qp'v'j g'hwcpq uwi ct "v'ngcf "v'j g'hwcpqr { tcp'f gtxcvkxg **53a**"kp s wcpvkvkxg" { kgrf "Uej go g'35+*J cs wg g'v'c'03; ; +0 Wpf gt "kf gp'ecv'eqpf k'kqp"v'j g'o g'v' { n'cpcqi wg **52b** i cxg'v'j g'hwcpqr { tcp'f gtxcvkxg **53b**"kp"; 2' " { kgrf 0 J qy gxgt. 'cp'c'wgo r v'q'cppwrcv'cp'gki j v'o go dgtgf qzc/e { erg'qp"v'j g'hwcpq"uwi ct "d { "TEO "qh'v'j g'f kpgg **52c**'y kj "v'j g'ecv'c'uv'5'y cu'wpuweegu'hw'0

Cppwrcvqp'qhf'kxg'v'p'kpg/o go dgtgf 'tkpi u'y cu xgt { 'u'weegu'hw'qp'v'i n'eq't { tcp'qug'f gtxcvkxg"J cm g'v'c'03; ; +0Vj g'ngv'qpg **54a**"qp'tgcev'kqp"y kj "xkp { n o ci p'gukwo 'ej n'rtkf g'ch'qtf g'f'v'j g'eku/cf f k'kqp'r t'qf wev **55a**"kp"55' " { kgrf "cm'pi "y kj "v'j g'w'cpu/cf f k'kqp r t'qf wev **56a**"Uej go g'36+0Y j k'g'v'j g'w'cpu'f k'kpg **56a** h'ck'g'f "v'q"wpf g'ti q"TEO."v'j g'eku/cpc'qi wg **55a** underwent ring closure with Grubbs' catalyst **5**"kp d'gpl g'p'g"v'q'ch'qtf "e { em'p'g'v'p'g"cppwrcv'g"i n'eq'ug f g'tkx'cvkxg **57a**"kp"37' " { kgrf 0'Vj g'o g'v'j { n'v'gf eqo r q'w'pf **55b**"r t'g'r c't'g'f "h't'qo **54a**"r t'q'f we'g'f "v'j g' c'p'p'w'rc'v'g'f "u'wi ct **57b**"kp'o we'j 'k'o r t'q'x'g'f " { kgrf "*, : ' +0 Vj g'g'h'h'ek'g'p'v't'k'p'i "em'q'w't'g"q'h"v'j g'o g'v'j { n'v'gf eqo r q'w'pf **57b**"ku'c'w't'k'd'w'g'f "v'q"Vj q't'r g'k'p'i q't'f "v'f r g'g'h'g'ev"kp"y j k'ej "v'j g's'w'c'v'g't'p'c't { "eg'p't'g"dg'c't'k'p'i "v'j g'o g'v'j { n'i t'q'w'r "t'g'u't'k'ev"v'j g'f'g'i t'g'g'q'h'h't'g'g'f'q'o "q'h"v'j g'cm'g'p'g'ej k'p'o c'n'k'p'i "t'k'p'i "em'q'w't'g"o q't'g'g'h'h'ek'g'p'0'k'p' eq'p't'c'u'v'q'v'j g'h'c'k'w't'g'q'h'w'c'p'u/cf f k'k'q'p'r t'q'f wev **56**"v'q'wpf g'ti q"t'k'p'i "em'q'w't'g."v'j g'j k'j j g't'c'p'c'qi wg **58**. q'd'v'k'p'g'f "cu"v'j g'o k'p'q't' r t'q'f we'v'q'p'c'f f k'k'q'p'q'h'c'm' { n o ci p'gukwo "ej n'rtkf g"v'q"v'j g'ngv'qpg **54a**."e { erk'ug'f uo q'q'v'j n'f'v'j k'j "v'j g'ecv'c'uv'5"v'q'ch'q't'f "v'j g'w'c'p'u/h'w'ug'f e { em'j g'z'g'p'g'f g'tkx'cvkxg **59**"kp": 2' " { kgrf "Uej go g'37+0

Cppwrcvqp'q'h'eku/h'w'ug'f "ukz/. 'ug'x'g'p'/'c'p'f "g'k'i j v' o go dgtgf 'tkpi 'qp'v'q'i n'eq't { tcp'q'ug'y cu'h'q'w'p'f "v'q'd'g h'cekg'0'Vj g'f k'p'g'gu **60a-c**."q'd'v'k'p'g'f "cu"v'j g'o c'l'q't r t'q'f we'v'h't'q'o "c'f f k'k'q'p'q'h'c'r r t'q'r t'k'ev'g"cm'g'p' { n o ci p'gukwo "ej n'rtkf g"q't'd't'q'o k'f g'v'q"v'j g'ngv'qpg **54a**. e { erk'ug'f "uo q'q'v'j n'f'v'j j g'p'v't'g'c'v'g'f "y k'j "v'j g'ecv'c'uv'5



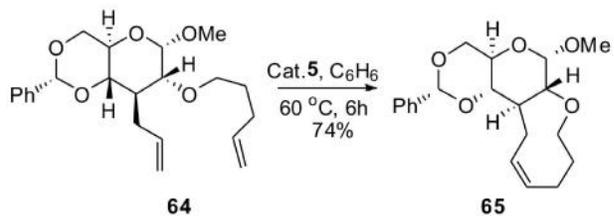
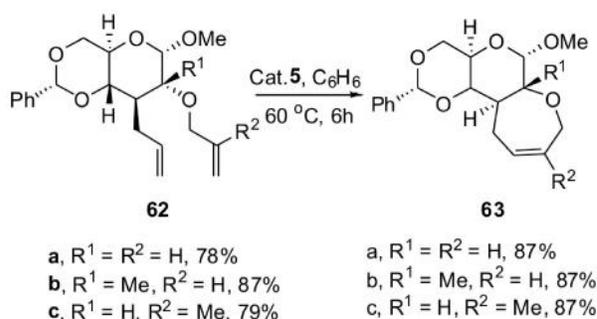
Scheme 15



Scheme 16

v'q'r t'q'f we'g'f "v'j g'eku/h'w'ug'f "ukz/. 'ug'x'g'p'/'c'p'f "g'k'i j v' o go dgtgf 'c'p'p'w'rc'v'g'f "r t'q'f we'v **61a-c**"kp": ; ' .': 9' c'p'f "74' " { kgrf u't'g'ur g'e'v'k'x'g'n' "Uej go g'38+0Uo q'q'v'j h'q't'o c'v'k'p' "q'h"v'j g'g'k'i j v'o go dgtgf "e'c't'd'q'e { erg. f k'h'h'ew'n'v'q'u { p'v'j g'uk'ug'd { "q'v'j g't' e { erk'uc'v'k'p'o g'v'j q'f u. k'u"p'q'v'g'y q't'v'j { 0'J qy gxgt."v'j g'f k'p'g'g **60d**"h'ck'g'f "v'q' r t'q'f we'g'f "v'j g'p'k'p'g/o go dgtgf 'tkpi "c'p'p'w'rc'v'g'f "r t'q'f we'v **61d**0'Q'p'n'f "k'p'v'g't'o q'ng'ew'r't' "o g'v'c'v'j g'uk'u'r t'q'f we'v'v'j cu q'd'ug't'x'g'f 0

Cppwrcvqp'q'h'o g'f k'wo "uk'z'g'f "q'z'c'e { erg'u"qp"v'q' i n'eq'r { tcp'q'ug'f g'tkx'cvkxg"y cu'c'n'q' c'ej k'x'g'f "]3: _ uo q'q'v'j n'f'v'j t'q'w'i j "TEO 0'f k'p'g'gu **62a-b**."t'g'r c't'g'f "h't'q'o v'j g'g'i n'eq'ug'f g'tkx'cvkxg **54a**."qp't'g'c'v'o g'p'v'y k'j "v'j g'ecv'c'uv'5"t'g'u'w'ng'f "k'p"t'k'p'i "em'q'w't'g"v'q'ch'q't'f "v'j g'q'z'g'r g'p'g'gu **63a-b**"kp": 9' " { kgrf "Uej go g'39+0



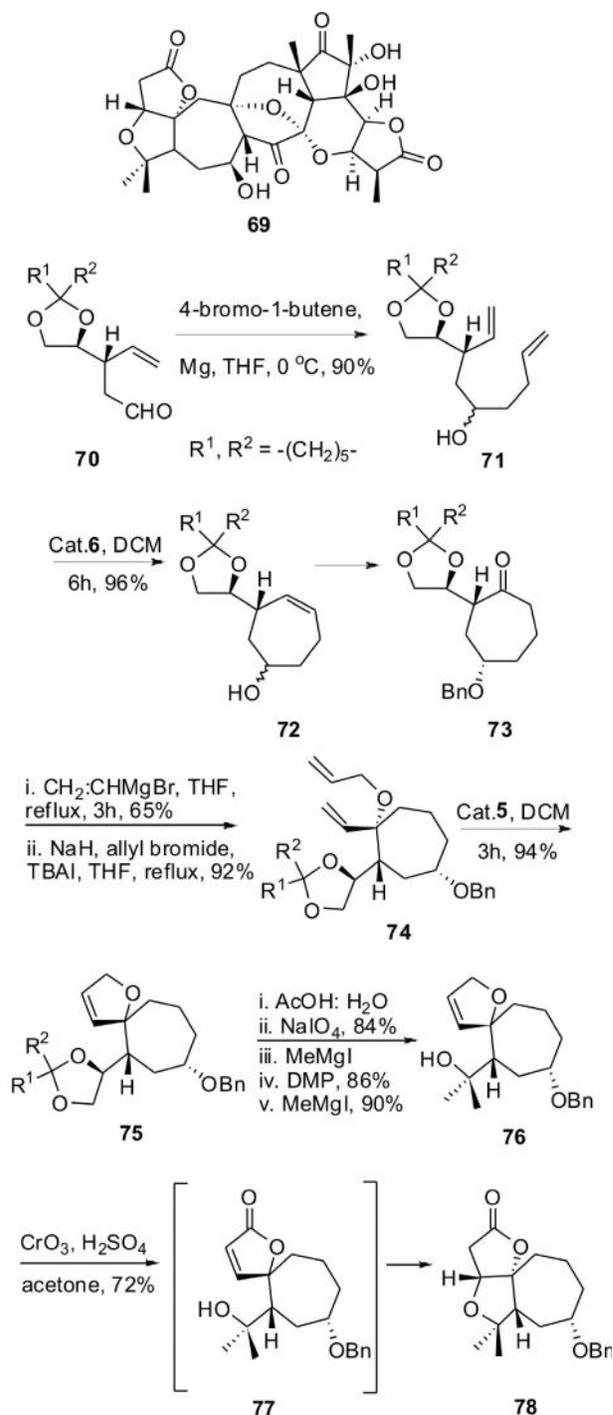
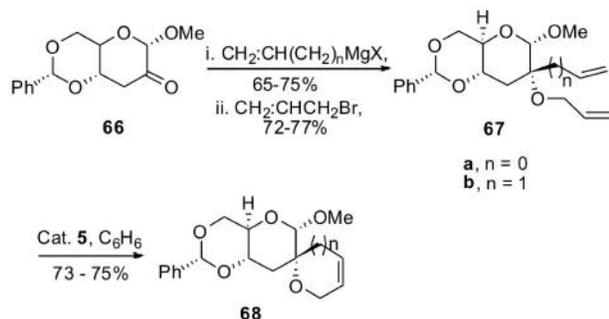
Scheme 17

Under identical condition the diene **64** afforded the nine-membered oxacycle **65** in 74% yield. The facile formation of nine-membered oxacycle is in stark contrast with the failure of RCM of the carbon chain containing analogue **60d** to form the nine-membered carbocyclic compound **61d**.

Spiro annulation also proceeded smoothly. The dienes **67a, b** were prepared from the glucose derivative **66** by addition of vinyl magnesium chloride (for **61a**) or allyl magnesium chloride (for **61b**) followed by etherification (NaH and allyl bromide) in very good yields (Scheme 18). Exposure of a benzene solution of the dienes **67a, b** with the catalyst **5** at 60 °C gave the spiro annulated products **68a, b** in very good yields.

We have used [19] RCM as the key step in the synthesis of A/B/C tricyclic ring systems present in densely functionalized highly structurally complex schisandra nortriterpenoids possessing a wide ranging bioactivity. Micrandilactone A **69** is a representative example of this family. The synthesis began with the preparation of the compound **73** (Scheme 19). RCM of the dienol **71**, prepared from the aldehyde **70**, with Grubbs II afforded the cycloheptenol **72** in 96% yield. The compound **72** was then converted to the cycloheptanone derivative **73** through a number of trivial steps. Cycloheptanone **73** was then elaborated to the diene **74** as depicted in Scheme 19.

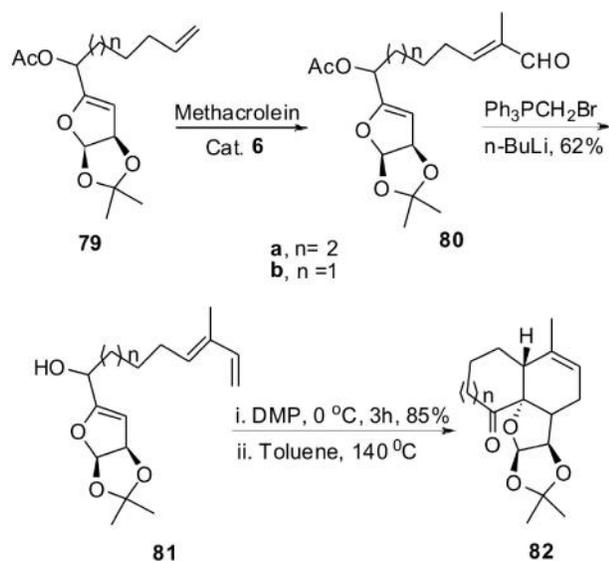
RCM of the diene **74** proceeded smoothly to form the spiro dihydrofuran derivative **75**. Transformation of the dihydrofuran **75** to **76** was trivial. CrO₃ induced oxidation of **76** proceeded through 1, 4-conjugate addition of *in situ* generated spiro butenolide **77** to afford the tricyclic lactone **78**,



structural motif present in the schisandra nortriterpenoids.

Cross Metathesis

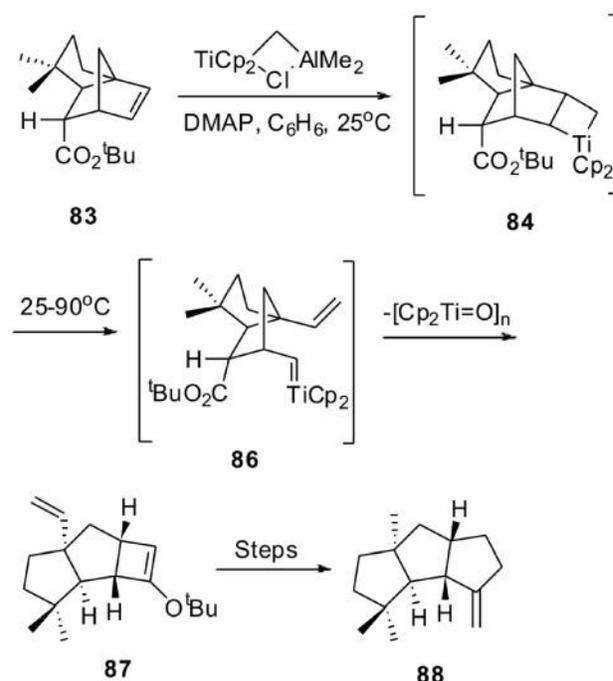
Cross metathesis (Cannon and Blechert 2003)



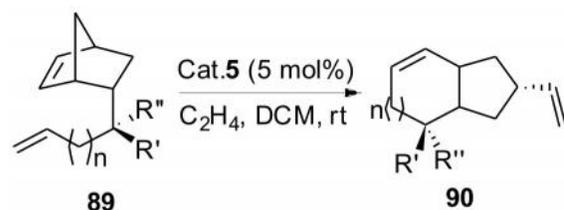
provides a mild high yielding route for diene synthesis. In connection to the synthesis of decalins and hydrindanes through intramolecular Diels-Alder reaction we developed (Mondal *et al.* 2013) a general protocol for synthesis of substrates containing dienophile as well as diene units using cross metathesis. Treatment of the diene **79a** with methacrolein in the presence of Grubbs' catalyst **6** afforded the unsaturated aldehyde **80a** in 95% yield (Scheme 20). Under identical condition the diene **79b** gave the unsaturated aldehyde **80b** in excellent yield. It may be noted that cross metathesis took place only at the terminal double bond. Wittig olefination of the aldehyde moiety in **80a** and **80b** then afforded the dienes **81a** and **81b** respectively. Oxidation of **81a** with DMP gave directly the trans-decalin derivative **82a** in excellent yield. However, the trienone obtained after DMP oxidation of **81b** required heating at 140 °C for Diels-Alder reaction to produce a mixture of cis- and trans-hydrindane derivatives **82b**.

3. Domino Ring Opening (RO)-Ring Closing Metathesis (RCM)

Domino processes (Tietze and Beifus 1993) involving a series of organic transformations provide enormous possibilities for rapid creation of molecular complexity. Ring closing, ring opening and cross metathesis generally occur under identical reaction condition. Thus appropriately designed substrates on



treatment with a suitable catalyst may undergo a sequence of ring opening and ring closing metathesis reaction to lead to polycyclic structures in a single pot (Holub and Blechert 2007). This concept was demonstrated by Grubbs and co-workers (1990) in an approach to the synthesis of capnellene **88**. The norbornene derivative **83** when treated with Tebbe reagent undergoes ring opening through the titanacyclobutane **84** to give titanium carbene complex **86** (Scheme 21). The latter on reaction with the proximal carbonyl group afforded the tricycle **87** which was subsequently transformed to capnellene **88**.

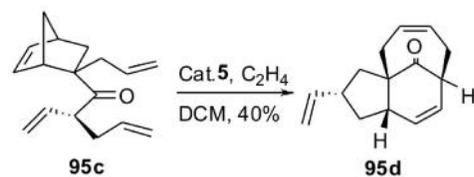
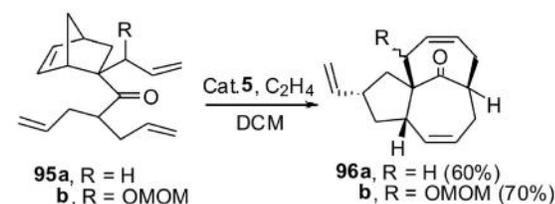
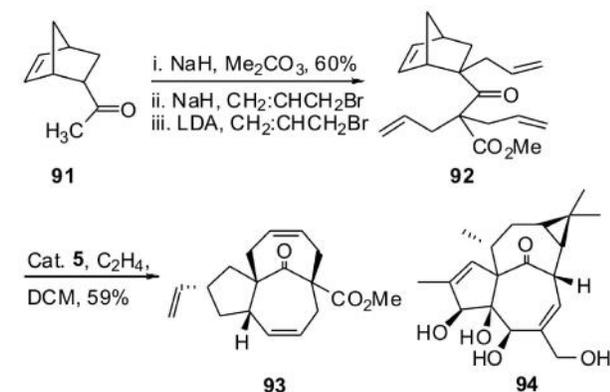


- a, n = 0, R' = H, R'' = OTBS, 80%
- b, n = 1, R' = H, R'' = OTBS, 88%
- c, n = 2, R' = H, R'' = OTBS, 75%
- d, n = 3, R' = OTBS, R'' = H, 83%

Scheme 22

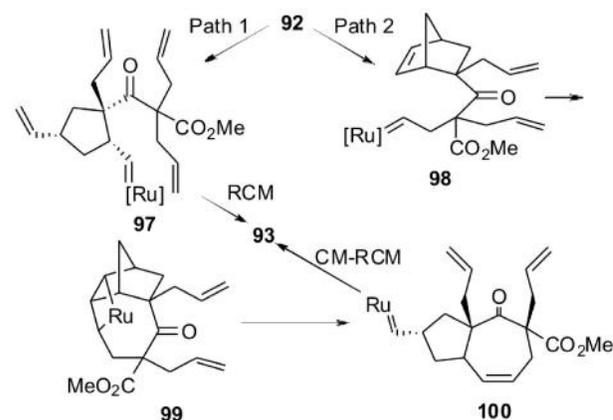
After the advent of the Grubbs ruthenium catalysts, Strategies and Blechert (1998) employed the concept described by Grubbs to construct fused ring systems of various sizes. Treatment of the norbornene derivatives **89a-d** with the catalyst **5** in dichloromethane under ethylene atmosphere resulted in smooth domino ROM-RCM-CM processes to lead to the fused bicycles **90a-d** in 75-88% yields (Scheme 22).

We have extensively employed domino ROM-RCM-CM processes to construct polycyclic carbon networks with high degree of molecular complexity. The norbornene derivative **92**, prepared from the known Diels-Alder adduct **91**, when subjected to metathesis with the catalyst **5** under ethylene atmosphere, produced the tricyclo [7.4.1.0^{1,5}] tetradecane **93** in 59% yield (Scheme 23) (Malik and Ghosh 2007). The compound **93** having “out-out” bicyclo [4.4.1] undecene represents the tricyclic framework of the anti-cancer and anti-HIV active highly strained tetracyclic diterpene ingenol **94**. The most remarkable feature of this protocol is the direct

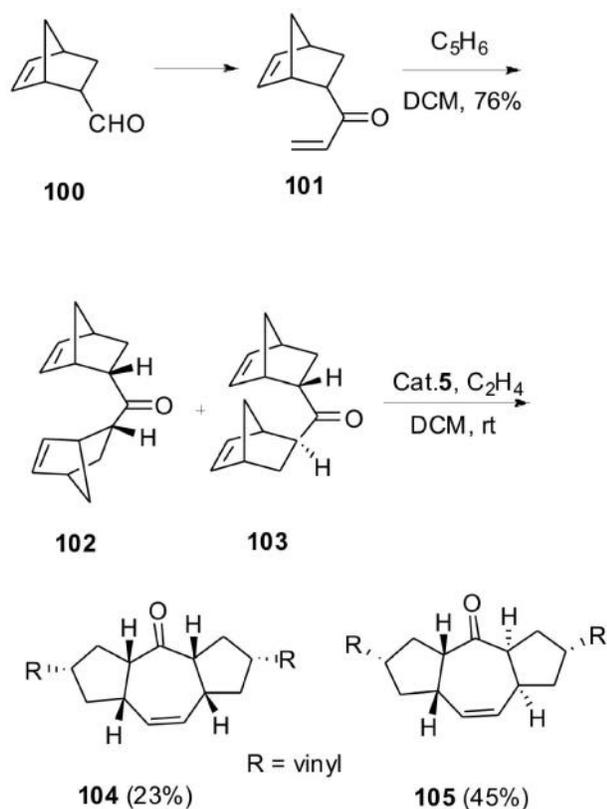


Scheme 23

access to this structurally complex bridged tricyclic skeleton of ingenol, which otherwise has been prepared with difficulty through multi-step processes. Since norbornene derivatives are easily available through Diels-Alder reaction of cyclopentadiene derivatives, a sequence of Diels-Alder reaction and metathesis thus offers an attractive route for rapid access to highly complex structures. Successful synthesis of the analogues **96a,b** from metathesis of the norbornene derivatives **95a,b** illustrates the generality of the domino metathesis protocol. Similarly the norbornene derivative **95c** provided the tricycle **95d** in 40% yield. The formation of the tricyclo [7.4.1.0^{1,5}] tetradecenes may be explained by two different reaction paths (Scheme 24). Metathesis may initiate at the norbornene double bond to produce regioselectively the ruthenium carbene intermediate **97** (path 1). Two consecutive RCM then gives rise to the product **93**. This regioselectivity may be attributed to a keto-directed addition of the catalyst from the endo face. ROM may also take place to provide a regioisomer of **97** which on cross metathesis with ethylene followed by two consecutive RCM steps provides **93**. An alternative path may involve initiation of metathesis at one of the gem-diallyl moiety to produce the Ru-carbene **98**. An intramolecular cycloaddition of Ru-carbene to norbornene double bond may give rise to the metalla-cyclobutane **99**. Cycloreversion of **99** leads to the Ru-carbene **100**. CM of **100** with ethylene followed by RCM involving the residual allyl units finally led to **93**.



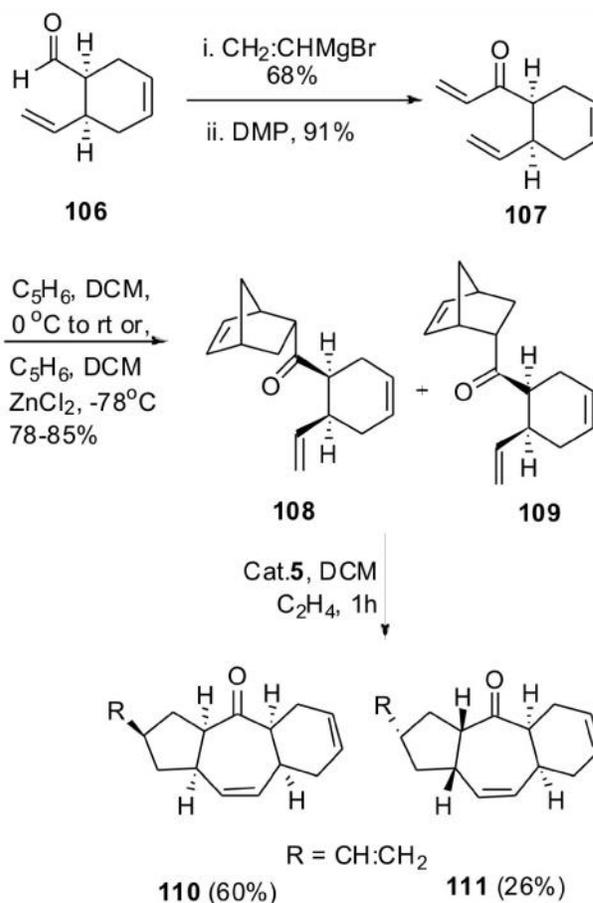
Scheme 24



Scheme 25

The sequential Diels-Alder reaction of cyclopentadiene and ROM-RCM cascade of the resulting norbornene derivative can be extended for the synthesis of fused tricyclic systems too. The enone **101**, prepared from the aldehyde **100**, on Diels-Alder reaction with cyclopentadiene afforded an inseparable mixture of adducts **102** and **103** in 1:2 ratio respectively (Scheme 25) (Malik C K and Ghosh S, 2007). When this mixture was subjected to metathesis with the catalyst **5**, the *cis-syn-cis* and *cis-anti-cis* 5/7/5 fused tricycles **104** and **105** were obtained in 23% and 45% yields respectively.

In a similar fashion condensed 5/7/6 tricyclic system can be constructed as depicted in Scheme 26 (Malik C K *et al.* 2009). Diels-Alder reaction of the enone **107**, prepared from the aldehyde **106**, with cyclopentadiene afforded a mixture of adducts **108** and **109** in excellent yield. Metathesis of this mixture with the catalyst **5** proceeded smoothly to produce the fused 5/7/6 tricyclic compounds **110** and **111** in 60% and 26% isolated yields respectively. Direct synthesis of 5/7/6 tricycles is of great significance as



Scheme 26

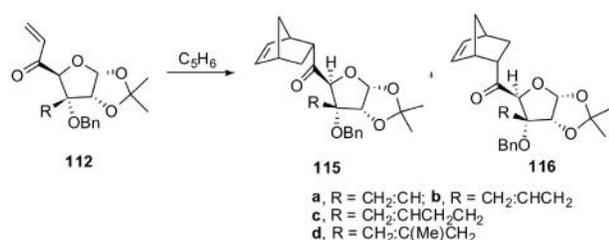
this unit represents the core structure of a number of highly biologically active natural products.

In both the cases presented above it may be noted that a mixture of *cis-syn-cis* and *cis-anti-cis* tricyclic systems were obtained as Diels-Alder reaction proceeded non-stereoselectively arising from addition of the diene from *Re*-face as well as from *Si*-face of the enone double bond. Some selectivity was observed as addition of the diene from *Re*-face was blocked by the *syn* alkyl chain having the alkene unit on the centre next to the carbon bearing the enone unit. The major product thus arose from addition of the diene from the *Si*-face.

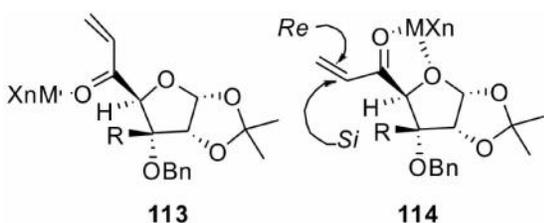
It was envisaged that replacement of the carbocyclic ring in the dienophile by a sugar ring may direct addition from *Re*-face of the enone moiety if the Diels-Alder reaction is carried out in presence of a Lewis acid as catalyst. The dienophile **112** was

Table 1: Diels-Alder reaction of enones **112 with cyclopentadiene**

Entry	Dienophile	Products	Yield
1	112a	115a+116a	88% (3:1) ^a 84% (1:100) ^b
2	112b	115b+116b	89% (4:1) ^a 86% (1:100) ^b
3	112c	115c+116c	89% (4:1) ^a 87% (1:100) ^b
4	112d	115d+116d	90% (16:1) ^a 88% (1:100) ^b

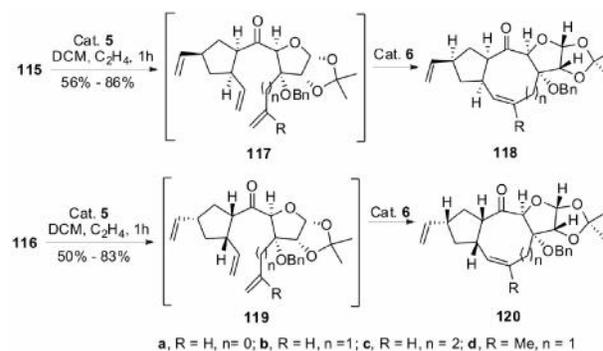
^aTHF, 0°C, ^bZnCl₂, DCM, -78°C

chosen. Since *Re*-face is blocked by the adjacent bulky group “R”, diene would add from the *Si*-face to give **115** as the major product. Indeed, reaction of the dienophiles **112a-d** with cyclopentadiene without any catalyst gave adducts **115a-d** and **116a-d** with the former predominating (Table 1) (Scheme 27). The ratio of adducts **115** and **116** increased with increase in size of the “R” group. Thus in going from **115a** to **115d** the ratio increased from 3:1 to 16:1. It was predicted that the σ bond linking the enone moiety in the Lewis acid (MX_n)-complexed dienophile **113** would rotate due to increased eclipsing interaction with the substituent “R” and undergo chelation with the sugar ring oxygen to form a rigid bidentate chelate complex **114** (Fig. 3). In this complex the *Si*-face is

**Fig. 3:**

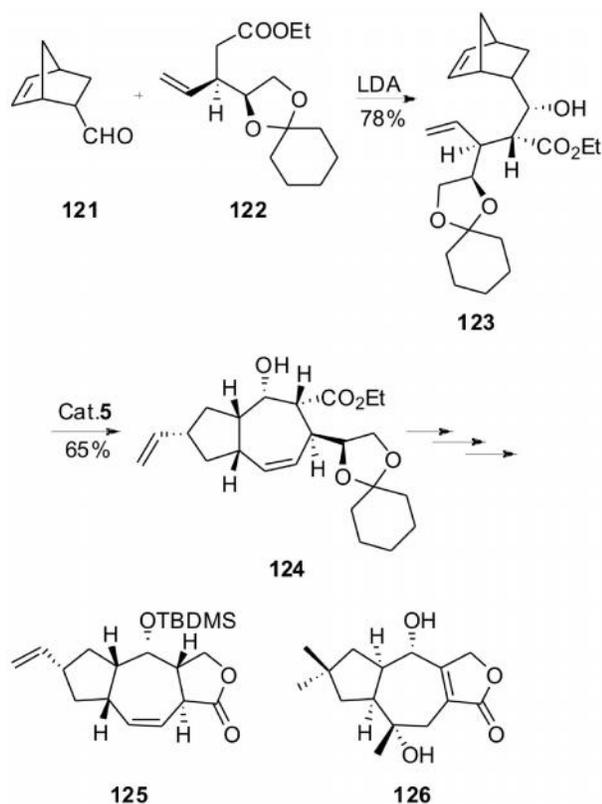
blocked by the substituent “R”. Addition was then expected to take place on the *Re*-face resulting in reversal of facial selectivity. As a matter of fact, when ZnCl₂ was used as catalyst in the above Diels-Alder reaction, adducts **116a-d** were obtained exclusively arising through addition on the *Re*-face of the chelated complex **114** in which the *Si*-face is blocked by “R”. Thus Lewis acid in these examples is simply changing the orientation of the *Re*-face of the enone **112** from hindered to unhindered position through rotation during formation of the chelate.

Attempted ROM-RCM of the norbornene derivative **115a** with the catalyst **5** led to the ring opened products **117a** in 92% yield. ROM-RCM of **115a** with the more reactive catalyst **6** caused extensive polymerization. However, when the ring opened product **117a** was treated with the catalyst **6** smooth ring closure took place to produce oxatricycle **118a** in 86% yield. Based on this observation a protocol involving treatment of the norbornene derivatives first with the catalyst **5** till the disappearance of starting materials and appearance of the ROM product (TLC) followed by treatment of the resulting reaction mixture with the catalyst **6** led to ROM-RCM to afford the tricyclic compounds **118a,b,d** and **120a, c** in very good yields (Malik *et al.* 2009). Compounds **115c** and **116b** gave directly the nine-membered and eight-membered carbocyclic derivatives **118c** and **120b** respectively in 1h with the catalyst **5** in excellent yields. Thus a sequence of face selective Diels-Alder reaction of the dienophile **112** with cyclopentadiene and ROM-RCM cascade of the resulting norbornene derivatives offered a general expedient approach for the synthesis of

**Scheme 28**

densely functionalised fused tricycles with seven-, eight- and nine-membered rings. The most notable feature of this protocol is the construction of both cis-syn-cis and cis-anti-cis fused tricyclic structures. The sugar residues in these compounds can be modified to make five- or six-membered carbocycles providing opportunity to produce linearly fused tricarbo-cyclic systems.

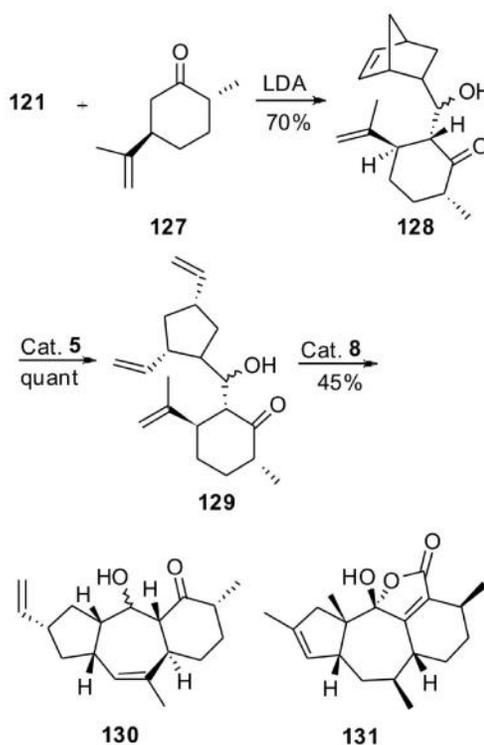
Lactaranes are a family of sesquiterpenes having a linearly fused tricyclic system. Lactarorufin A **126** is a representative example. Lactaranes possess wide ranging biological activities such as antifeedant, antimicrobial and mutagenic. We have extended [28] the domino ROM-RCM protocol for rapid construction of the core tricyclic lactone structure of lactaranes as depicted in Scheme 29. The synthesis starts with diastereoselective condensation of the known aldehyde **121** with the enolate generated from the ester **122** to give the hydroxy-ester **123**. Treatment of this ester with the Ru-catalyst **5** at rt led to tandem RO-RCM to afford the highly functionalized



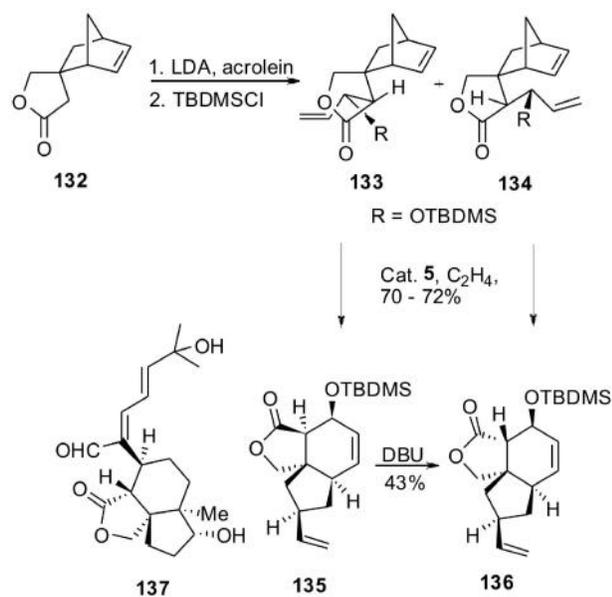
Scheme 29: Approach to lactaranes

hydroazulene derivative **124** in excellent yield. The compound **124** was then transformed through a number of steps to the tricyclic lactone **125** present in lactarorufin A **126**.

Caribenol A **131**, a nor-diterpene, exhibits strong inhibitory activity against *Mycobacterium tuberculosis*. It also exhibits weak *in vitro* antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* W2. We have developed (Mondal *et al.* 2009) a convergent asymmetric route to caribenol A using a RO-RCM of a norbornene derivative as the key step. Condensation of the aldehyde **121** with the enolate generated from dihydrocarvone **127** led to the formation of the adduct **128** (Scheme 30). The norbornene derivative **128** on treatment with the Grubbs first generation catalyst **5** failed to produce the expected RO-RCM product **130**. Rather under this condition only the ring opened product **129** was obtained in quantitative yield. The ring opened product **129** when treated with Hoveyda-Grubbs 2nd generation catalyst **8**, smooth ring closure took place to afford the tricycle **130**. The compound



Scheme 30: Approach to caribenol A



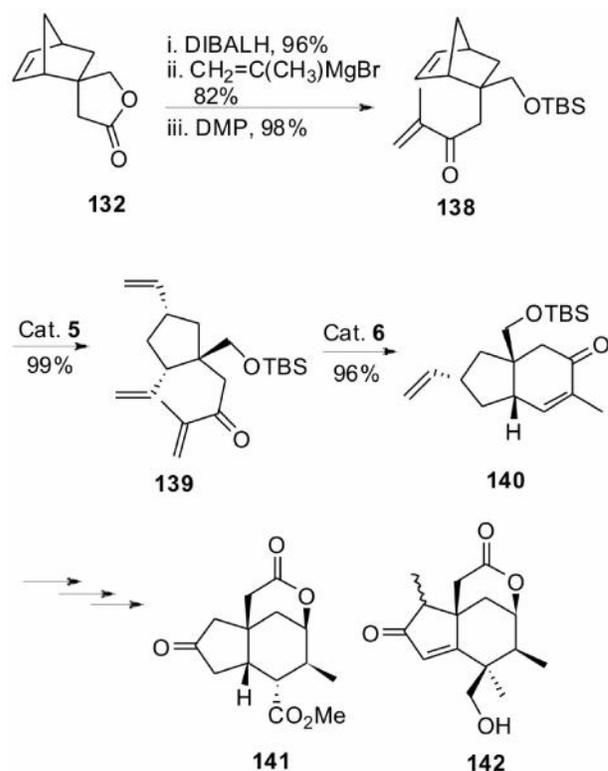
Scheme 31: Approach to umbellactal

130 closely resembles the tricyclic unit present in caribenol A **131**.

ROM-RCM sequence of norbornene derivatives can be extended for the synthesis of angularly annulated ring system also (Maity and Ghosh 2009). The cytotoxic diterpene umbellactal **137** is an angularly fused tricyclic lactone. The synthesis of its core structure is outlined below (Scheme 31). Reaction of lithium enolate of the lactone derivative **132** with acrolein followed by silylation and chromatographic separation afforded the pure products **133** and **134** in 50% and 19% yields respectively.

Metathesis of the silyl ether **133** and **134** with the catalyst **5** gave the tricyclic lactones **135** and **136** in 72% and 70% yields respectively. The trans fused lactone **135** could be isomerized easily to the cis fused lactone **136**. The silyl ether **136** represents the highly functionalized tricyclic skeleton present in umbellactal **137**.

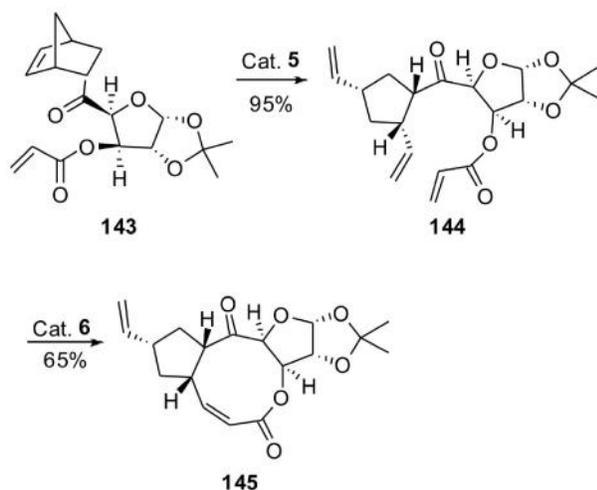
Sesquiterpenes of the seco-prezizane type such as minwanenones **142** exhibit bioactivity profile ranging from neurotoxicity to promoters of neurite. A hydrindane system with a bridged lactone/lactol is the core structure of this family. We have demonstrated that ROM-RCM of an appropriately designed norbornene derivative leads smooth



Scheme 32: Approach to minwanenones

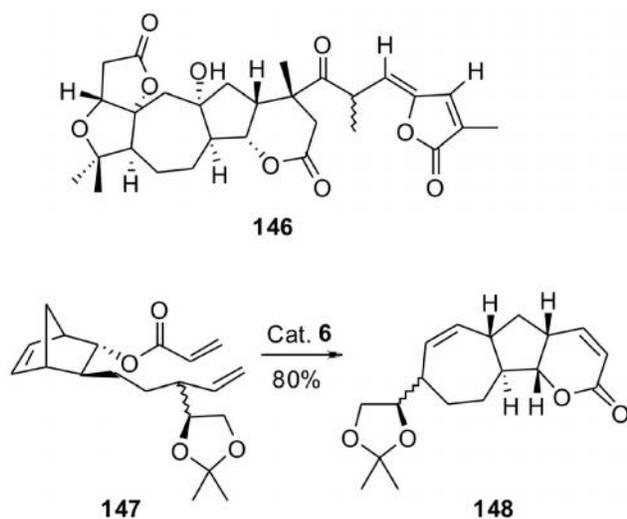
construction of the core structure (Scheme 32) (Yadav *et al.* 2011). The required norbornene derivative **138** was easily prepared from **132**. Metathesis of **138** with the catalyst **5** produced the ring opened product **139** in quantitative yield. Ring closure of **139** was then achieved with the Grubbs 2nd generation catalyst **6** to produce the hydrindane derivative **140** in excellent yield. Compound **140** was then transformed to the tricyclic bridged lactone **141**. This compound is structurally related to minwanenones **142**. Thus ROM-RCM sequence led to an easy access to the family of seco-prezizanes.

Synthesis of nine-membered oxa-cycles is a difficult task to achieve. This ring system is present in a large number of natural products. Fused ring system having nine-membered lactone could be achieved smoothly by ROM-RCM of norbornene derivative. Metathesis of the norbornene derivative **143** with the catalyst **5** provided the ring opened product **144** which underwent smooth ring closure with the catalyst **6** to afford the fused tricyclic system **145** containing nine-membered ring in overall excellent yield (Scheme 33) (Malik *et al.* 2009).



Scheme 33: Synthesis of fused nine-membered lactone

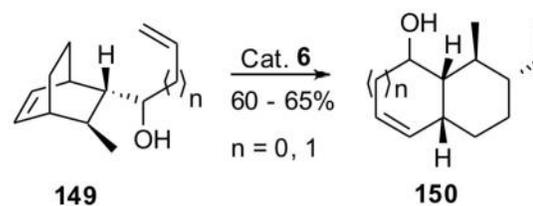
The nor-triterpenoids schintrialactones **146** belonging to *Schisandraceae* family with high biological activity profile pose considerable synthetic challenge due to their structural complexity. Domino metathesis provided an expedient route for the construction of the central tricyclic ring in a single step (Matcha *et al.* 2010). The sequence involves a ring opening metathesis-bidirectional ring closing metathesis of the norbornene derivative **147** with the catalyst **6** to provide the C/D/E ring system **148** present in schintrialactones **146** (Scheme 34).



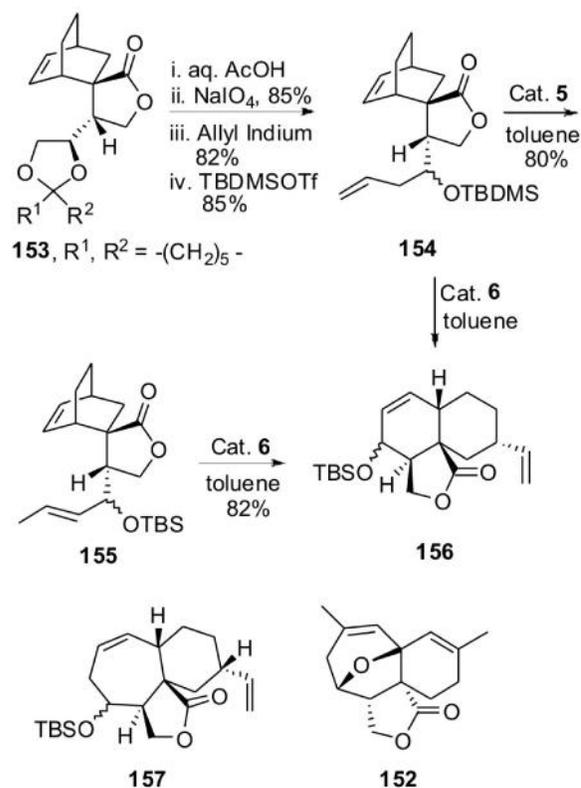
Scheme 34: Approach to Schintrialactones

4. Ring Opening-Ring Closing Metathesis of Bicyclo [2.2.2] Octenes

From the above discussion it is clear that employing ring opening metathesis of bicyclo [2.2.1] heptenes in combination with ring closing metathesis a variety of structural patterns having a fused five-membered ring can be synthesised. ROM-RCM of appropriately constructed bicyclo [2.2.2] octenes is thus expected to produce ring system with a six membered ring. Although Hagiwara *et al.* (2002) was unsuccessful in ring opening of bicyclo [2.2.2] octenes through metathesis, Chandler and Phillips 2005 have successfully constructed hydrindanes and decalins through ROM-RCM of bicyclo [2.2.2] octenes (Scheme 35).



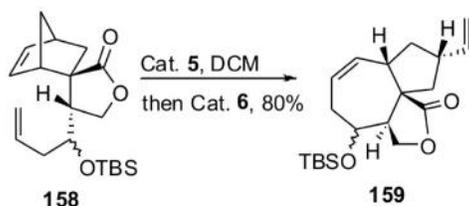
Scheme 35



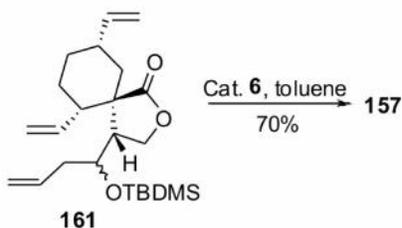
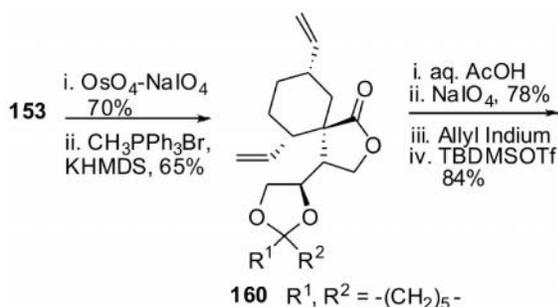
Scheme 36: ROM-RCM of bicyclo [2.2.2] octene derivative

In connection to a synthesis of the sesquiterpene anthecularin **152**, we planned to employ ROM-RCM of the bicyclo [2.2.2] octene derivative **154** prepared from the lactone **153** (Scheme 36). Surprisingly metathesis of **154** with the catalyst **6** provided the tricyclic lactone **156** having a six-membered ring instead of the expected product **157**. Compound **156** arose through metathesis of the isomerized alkene **155** as demonstrated by transformation of **154** to **155** with Grubbs 1st generation catalyst **5** and subsequent treatment of **155** with Grubbs 2nd generation catalyst **6**.

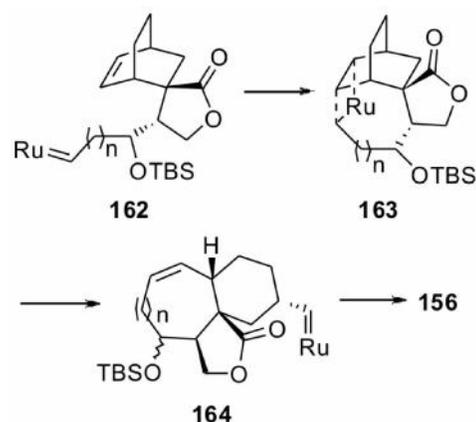
In contrast to this observation the norbornene analogue **158** on sequential treatment with the catalyst **5** and then with the catalyst **6** produced the tricyclic lactone **159** with seven-membered ring (Scheme 37) [36]. Further, it was interesting to note that the ring opened product **161**, prepared from **153** through a non-metathetic path (Scheme 38), underwent smooth ring closure when treated with the catalyst **6**. This indicated that inertness of the bicyclo[2.2.2]octene derivative **154** to undergo ring opening probably led



Scheme 37: ROM-RCM of bicyclo [2.2.1] heptenes



Scheme 38



Scheme 39: Plausible reaction course

to isomerization of the double bond in the side chain to produce **155**. The latter then underwent domino metathesis to produce the decalin system **156** with the catalyst **6**.

The formation of the six-membered ring rather than the expected seven-membered ring from metathesis of **154** may be attributed as follows (Scheme 39). Initially, the Ru-catalyst reacts with the alkene unit in the side chain of the compound **154** to form the new Ru-carbene **162**. This adds intramolecularly to the bridged olefin to form the metallacyclobutane **163**. Cycloreversion then generates the carbene **164** which on reaction with ethylene leads to the product **156**. The formation of ruthena-cyclobutane **163** ($n = 1$) required for the formation of the 7/6 bicyclic system is probably entropically unfavourable compared to those required for the formation of decalins such as **163** ($n = 0$). Thus product development drives isomerization of the double bond in **154** to **155** which subsequently undergoes ring opening-ring closing metathesis to lead to the product **156**.

5. Conclusion

A brief account on various types of olefin metathesis reactions has been presented. It includes application of ring closing metathesis in the synthesis of natural products and related structures. Domino metathesis involving ring closing metathesis-ring opening metathesis of bicyclo [2.2.1] heptene and bicyclo [2.2.2] octene derivatives for rapid construction of

complex molecular structures has also been described.

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