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Synthetic studies on taxanes: A domino–enyne metathesis/Diels–Alder approach to the AB-ring

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Abstract. A domino enyne cross-metathesis/intramolecular Diels–Alder reaction has been successfully used to synthesize a bicyclo[5.3.1] undecene, corresponding to AB-ring of taxol without the gem dimethyl group.

Keywords. Taxol; RCM; Grubbs catalyst; IMDA; Anticancer; Domino reaction.

1. Introduction

Taxol® (Paclitaxel: **1**), a remarkable cytotoxic diterpene having a complex molecular architecture, was first isolated from the bark of the Pacific yew tree, *Taxus brevifolia*, in 1967 by Wall and Wani, and the structure was elucidated in 1971 by the combination of X-ray studies and ^{1}H NMR analysis.[1] It was identified as the first member of the novel group of anticancer agents (figure 1), which promotes the assembly of the proteins α- and β-tubulin into microtubules and disturbs the polymerization–depolymerization dynamics by making the microtubules extremely stable. This makes the cell division impossible, resulting in cell death. This novel mechanism of taxol was in contrast to the existing anticancer drugs, viz. colchicine, podophyllotoxin and dolastatins, which bind to free tubulin and interrupt the growth of microtubules.[2] In view of the importance of the biological activity and scarce availability, many groups actively pursued strategies that aimed at the chemical synthesis of taxol. The potential problems anticipated in the synthesis are: (a) construction of a highly distorted and functionalized ABC-tricarbocyclic structure and (b) control of stereochemistry at highly congested asymmetric centers. Regardless of these problems, six synthetic groups have achieved the total synthesis of taxol using a variety of approaches.[3–8]

These syntheses were landmarks in the field of organic synthesis and the approaches for the construction of the basic skeleton of taxol could be divided into three types: (a) elaboration of naturally occur ring terpenes to the AB ring system of taxol by epoxy-alcohol fragmentation, e.g. total synthesis by Holton *et al.*[3] and by Wender *et al.*[6] (b) convergent strategies including a B-ring closure reaction of connected A–C ring system, e.g. total synthesis by Nicolaou *et al*,[4] Danishefsky *et al.*[5] and the Kuwajima group[7] and (c) a unique pathway to taxol core, starting with an acyclic precursor to form B-ring, executed by the Mukaiyama group.[8]

Unfortunately, even the shortest synthesis[6] of taxol known to date involves 37 steps with an overall yield of approximately 0·4%, which made the chemical synthesis of taxol less impressive on industrial scale. Gratifyingly, the semi synthesis of taxol from 10-deacetylbaccatin III (10-DAB) solved its supply problem as 10-DAB could be easily isolated from the leaves and twigs of the European yew, *Taxus baccata*, at approximately 0·1% by dry weight, without creating any environment hazards.[9] The relative ease in accessing the taxol through semi synthesis subdued the impact of total synthesis of taxol on its supply problems. On the other hand, synthesizing the analogues of taxol with less molecular complexity and comparable cytotoxicity to the parent molecule is an attractive target and also those analogues which are not available from natural sources but derived through chemical synthesis could be of biological interest.

2. Experimental

2.1 *General*

Unless and otherwise noted, all starting materials and reagents were obtained from commercial supp-

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liers and used after further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl and toluene from sodium. N,N- dimethyl formamide was distilled from $MgSO_4$. Dichloromethane, hexane and pyridine were freshly distilled from calcium hydride. All solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried in oven at 100°C for 12 h. Air and moisture sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Flash chromatography was performed using silica gel (100–200 mesh, Aceme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0·25 mm E. Merck silica plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotation was recorded on Jasco DIP-370 or Autopol IV digital polarimeter. IR spectra were recorded from Thermo Nicolet Avater 320 FT–IR and Nicolete Impact 400 machine. Mass spectra were obtained with Waters Micromass-Q-Tof micro^{TM} (YA105) spectrometer. ^{1}H and ^{13}C NMR spectra were recorded either on Varian AS 400 or Varian ASM 300. Values are listed as chemical shift, multiplicity (*s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *m*, multiplet; *dd*, doublet of doublet; *bs*, broad singlet), number of protons and coupling constant in hertz (Hz).

2.1a *(4S,5S,6S)-1-(6-Methoxy-2,2-dimethyl-6-vinyl-*tetrahydrofuro[3,4-d][1,3]dioxol-4yl)-ethane-(S)-1,2-*diol (**10**):* To a solution of mannose diacetonide **9** (3·12 g, 12 mmol) in dry THF (72 mL), at 0°C was added vinylmagnesium bromide (1·0 M in THF, 36 mL, 36 mmol) drop-wise. After stirring at 0°C for 2 h, the reaction mixture was allowed to attain room temperature and stirred for 12 h. The reaction was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give a residue which was purified by silica gel chromatography (40%, EtOAc/hexanes) to afford a mixture of diol (3·1 g, 90%) and traces of its epimer as colourless oils which solidified on storage at 0°C. R_f = 0·6 (2 : 3 ethyl acetate/hexanes); IR (neat) 3405, 3098, 1643, 1068 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5·97 (*ddd*, 1 H, *J* = 17·7, 10·2, 5·1 Hz, =C<u>H</u>), 5·47–5·25 (*m*, 2 H, C<u>H</u>$_2$=), 4·79 (*dd*, 1 H, *J* = 6·0, 3·6 Hz, C<u>H</u>), 4·58 (*d*, 1 H, *J* = 6·6 Hz, C<u>H</u>), 4·42–4·32 (*m*, 2 H, C<u>H</u>$_2$), 4·18–4·00 (*m*, 3 H, C<u>H</u> and CH$_2$), 3·89–3·85 (*m*, 1 H, C<u>H</u>), 3·49 (*d*, 1 H, *J* = 6·6 Hz, C<u>H</u>), 1·52 (*s*, 3 H, C<u>H</u>$_3$), 1·39 (*s*, 3 H, C<u>H</u>$_3$), 1·37 (*s*, 3 H, C<u>H</u>$_3$), 1·34 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 133·7, 118·6, 111·7, 104·7, 85·3, 80·9, 75·4, 70·0, 37·8, 26·8, 26·2.

To a stirred suspension of MnO_2 (15.1 g, 173.6 mmol) in 100 mL of dry CH_2Cl_2, a solution of above diol (2·5 g, 8·68 mmol), in 10 mL of CH_2Cl_2 was added drop-wise and stirred for 12 h at room temperature. TLC of the reaction was monitored until disappearance of the starting material. The mixture was filtered through a sintered glass funnel, concentrated *in vacuo* and purified by silica gel chromatography (33%, EtOAc/hexanes) to afford a lactol (2·3 g, 92%) as a colourless oil. R_f = 0·6 (1:4 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = +35·8 (*c* 1·7, $CHCl_3$); IR (neat) 3409, 3104, 1737, 1637 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6·06 (*dd*, 1 H, *J* = 17·7, 11·1 Hz, C<u>H</u>=), 5·63–5·57 (*m*, 1 H, C<u>H</u>=), 5·42–5·38 (*m*, 1 H, C<u>H</u>=), 4·92 (*dd*, 1 H, *J* = 6, 3·6 Hz, C<u>H</u>), 4·50 (*d*, 1 H, *J* = 5·7 Hz, C<u>H</u>), 4·51–4·44 (*m*, 1 H, C<u>H</u>), 4·21 (*dd*, 1 H, *J* = 7·5, 3·6 Hz, C<u>H</u>), 4·18–4·05 (*m*, 2 H, C<u>H</u>$_2$), 3·16 (*br s*, 1 H, O<u>H</u>), 1·52 (*s*, 3 H, C<u>H</u>$_3$) 1·50 (*s*, 3 H, C<u>H</u>$_3$), 1·42 (*s*, 3 H, C<u>H</u>$_3$), 1·36 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136·3, 117·4, 112·8, 109·1, 104·4, 86·7, 80·3, 79·2, 73·3, 66·6, 26·8, 25·8, 25·2, 24·4; LRMS (ES) $[M + Na]^+$ 309·1693; HRMS (ES) calcd. for $C_{14}H_{22}O_6Na$ *m/z* 309·1314, found *m/z* 309·1315.

To a stirred solution of the above lactol (650 mg, 2.27 mmol), in dry methanol (20 mL) was added PPTS (1·14 g, 4·5 mmol) and the mixture was stirred for 12 h at room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were dried over anhydrous sodium sulphate and evaporated under reduced pressure to give a residue which was purified by silica gel chromatography (50%, EtOAc/hexanes) to afford **10** (520 mg, 88%) as a colourless oil. R_f = 0·2 (2 : 3 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = +79.5 (*c* 0·83, $CHCl_3$); IR (neat) 3405, 3098, 2940, 1643, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71 (*dd*, 1 H, *J* = 17·6, 10·4 Hz, =C<u>H</u>), 5·52–5·44 (*m*, 2 H, C<u>H</u>$_2$=), 4·89 (*dd*, 1 H, *J* = 9·6, 4·0 Hz, C<u>H</u>), 4·48 (*d*, 1 H, *J* = 6·0 Hz, C<u>H</u>), 4·08–4·04 (*m*, 1 H, C<u>H</u>), 3·92–3·84 (*m*, 2 H, C<u>H</u>$_2$), 3·70 (*dd*, 1 H, *J* = 11·2, 6·0 Hz, C<u>H</u>), 3·13 (*s*, 3 H, OC<u>H</u>$_3$), 1·46 (*s*, 3 H, C<u>H</u>$_3$), 1·32 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132·3, 119·9, 113·0, 108·0, 86·4, 80·8, 76·9, 70·2, 64·6, 48·9, 26·1, 24·9; LRMS (ES) $[M + Na]^+$ 283·1418; HRMS (ES)

calcd. for $C_{12}H_{20}O_6Na$ *m/z* 283·1158, found *m/z* 283·1156.

2.1b *6-Methoxy-2,2-dimethyl-6-vinyl-tetrahydro-furo [3,4-d]-di-oxole-4-carbaldehyde (**11**)*: A suspension of silica supported $NaIO_4$ (4 g) in CH_2Cl_2 (5 mL) at room temperature was treated with the solution of diol **10** (0·5 g, 1.9 mmol) in CH_2Cl_2 (5 mL) and stirred for 2 h. After the solids were removed by filtration, filtrate was concentrated and the crude compound **11** was preceded further without purification. $R_f = 0.6$ (1 : 1 ethyl acetate/hexanes).

2.1c *1-(6-Methoxy-2,2-dimethyl-6-vinyl-tetrahydro-furo[3,4-d][1,3]dioxol-4-yl)-but-3-yn-1-ol (**12**):* A suspension of activated zinc and aldehyde **11** (440 mg, 1·71 mmol) in THF (8 mL) at room temperature was treated with a solution of propargyl bromide in THF (2 mL) and stirred for 3 h. After filtering the reaction mixture through a pad of Celite, the solvent was evaporated; the residue was dissolved in CH_2Cl_2 and then quenched with 10% aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2. The organic layer was washed (10% aqueous NH_4Cl solution), dried (Na_2SO_4), concentrated and purified by a flash column chromatography (11% EtOAc in hexanes) to afford **12** (0·29 g, 67% over two steps) as a white solid. $R_f = 0{\cdot}5$ (1 : 1 ethyl acetate/hexanes); m.p. = 70–71°C; $[\alpha]^{25}_D$ = 74·07 (*c* 1·08, $CHCl_3$); IR (KBr) 3354, 3298, 3021, 2994, 2952, 1375, 1375, 1218 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5·71 (*dd*, 1 H, *J* = 17·4, 10·8 Hz, =C<u>H</u>), 5·53–5·42 (*m*, 2 H, =C<u>H</u>$_2$), 4·91 (*dd*, 1 H, *J* = 5·7, 3·9 Hz, C<u>H</u>), 4·48 (*d*, 1 H, *J* = 5·7 Hz, C<u>H</u>), 4·14–4·08 (*m*, 1 H, C<u>H</u>), 3·88 (*dd*, 1 H, *J* = 8·4, 3·6 Hz, C<u>H</u>), 3·15 (*s*, 3 H, C<u>H</u>$_3$), 2·75–2·54 (*m*, 2 H, C<u>H</u>$_2$), 2·08 (*t*, 1 H, *J* = 2·7, ≡C<u>H</u>), 1·45 (*s*, 3 H, C<u>H</u>$_3$),1·32 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) 132·2, 119·8, 113·0, 107·8, 86·5, 80·5, 80·4, 79·6, 70·8, 67·8, 48·9, 26·1, 24·8, 24·4; LRMS (ES) $[M + Na]^+$ 291·1214; HRMS (ES) calcd. for $C_{14}H_{20}O_5Na$ *m/z* 291·1208, found *m/z* 291·1208; Anal· calcd. for $C_{14}H_{20}O_5$: C, 62·67; H, 7·51· Found: C, 62·247; H, 7·691.

2.1d *(tert-Butyl-[1-(6-methoxy-2,2-dimethyl-6-vinyl-tetrahydro-furo[3,4-d]dioxol-4-yl]-but-3-ynyloxy]-dimethyl-silane (**13**):* A solution of alcohol **12** (0·23 g, 0·86 mmol) in DMF at room temperature was treated with Immidazole (0·175 g, 2·58 mmol), TBSCl (0·155 g, 1·03 mmol), catalytic amount of TBAI and then warmed to 50°C. After stirred for 24 h at 50°C, the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was separated, dried (Na_2SO_4), concentrated and purified by a flash column chromatography (4% EtOAc in hexanes) to afford **13** (0·225 g, 83%). $R_f = 0{\cdot}7$ (1 : 9 ethyl acetate/hexanes); $[\alpha]^{25}_D = 38{\cdot}1$ (*c* 1·05, $CHCl_3$); IR (neat) 3314, 2934, 2857, 1650, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 5·68 (*dd*, 1 H, *J* = 7·7, 10·8 Hz, =C<u>H</u>), 5·49–5·39 (*m*, 2 H, =C<u>H</u>$_2$), 4·76 (*dd*, 1 H, *J* = 5·7, 3·6 Hz, C<u>H</u>), 4·44 (*d*, 1 H, *J* = 5·7 Hz, C<u>H</u>), 4·16–4·10 (*m*, 1 H, C<u>H</u>), 3·92 (*dd*, 1 H, *J* = 9·3, 3·9 Hz, C<u>H</u>), 3·15 (*s*, 3 H, C<u>H</u>$_3$), 2·57 (*dd*, 2 H, *J* = 3·6, 2·4 Hz, C<u>H</u>$_2$), 1·97 (*t*, 1 H, *J* = 3·0, ≡C<u>H</u>), 1·41 (*s*, 3 H, C<u>H</u>$_3$), 1·28 (*s*, 3 H, C<u>H</u>$_3$),0·9 (*s*, 9 H, 3 × C<u>H</u>$_3$), 0·13 (*s*, 3 H, C<u>H</u>$_3$), 0·10 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) 132·7, 119·3, 112·3, 107·7, 86·7, 81·3, 80·0, 79·6, 70·05, 67·5, 48·9, 26·1, 25·9, 25·1, 24·9, 18·2, –4·6, –4·8; HRMS (ES) calcd. for $C_{20}H_{34}O_5NaSi$ *m/z* 405·2073, found *m/z* 405·2091; Anal· calcd. for $C_{20}H_{34}O_5Si$: C, 62·79; H, 8·96· Found: C, 62·083; H, 9·282.

2.1e *(tert-Butyl-[1-(6-methoxy-2,2-dimethyl-6-vinyl-tetrahydro-furo[3,4-d]dioxol-4-yl]-3-methylene-pent-4-enyloxy]dime-thyl-silane (**14**):* Enyne **13** (0·078 g, 0·2 mmol) was dissolved in CH_2Cl_2 (62 mL) and ethylene gas was purged for 20 min. A solution of catalyst **17** (5 mol%) in 4 mL of CH_2Cl_2 was added slowly at room temperature and stirred for 3 h. The reaction mixture was filtered, concentrated and purified by a flash column chromatography (0·5% EtOAc in hexanes) to afford **14** (0·051 g, 64%). R_f = 0·8 (1 : 24 ethyl acetate/hexanes); IR (neat) 3020, 1650, 1216 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6·39 (*dd*, 1 H, *J* = 18, 11·2 Hz, =C<u>H</u>), 5·69 (*dd*, 1 H, *J* = 10·8, 17·6 Hz, =C<u>H</u>), 5·50–5·30 (*m*, 3H, 3 × =C<u>H</u>), 5·15–5·06 (*m*, 3 H, 3 × C<u>H</u>), 4·75 (*dd*, 1 H, *J* = 5·6, 3·6 Hz, =C<u>H</u>), 4·44 (*d*, 1 H, *J* = 5·6 Hz, C<u>H</u> of CH_2), 4·3 (*ddd*, 1 H, *J* = 16·4,8·4, 2·8 Hz, C<u>H</u> of CH_2), 3·71 (*dd*, 1 H, *J* = 7·6, 3·2 Hz, C<u>H</u>), 3·11 (*s*, 3 H, C<u>H</u>$_3$), 2·9 (*d*, 1 H, *J* = 14·4 Hz, C<u>H</u>), 4·44 (*dd*, 1 H, *J* = 14·4, 8·4 Hz, C<u>H</u>), 1·40 (*s*, 3 H, C<u>H</u>$_3$), 1·27 (*s*, 3 H, C<u>H</u>$_3$), 0·86 (*s*, 9 H, 3 × C<u>H</u>$_3$), 0·07 (*s*, 6 H, 2 × C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) 143·0, 139·1, 132·8, 119·4, 119·0, 113·8, 112·4, 107·5, 86·7, 81·9, 80·1, 68·4, 48·9, 37·9, 26·2, 24·9, 18·3, 1·1, –3·7, –4·8; LRMS (ES) $[M + Na]^+$ 433·3003; HRMS (ES) calcd. for $C_{22}H_{39}O_5Si$ $[M + 1]^+$ *m/z* 411·2570, found *m/z* 411·2567.

2.1f (*5-Ethynyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (**22**):* A solution of D (+) ribose acetonide **21**

(10 g, 52·3 mmol) in MeOH (250 mL) was treated with $NaBH_4$ (8·1 g, 213 mmol) in portion-wise at 0°C and the stirring was continued for 2 h before neutralizing with glacial AcOH at 0°C. After adjusting the pH to 7, water (150 mL) was added and treated with finely powdered $NaIO_4$ (20 g) at room temperature and the stirring was continued for further 3 h. After filtration, the solvent was evaporated and then the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (25% EtOAc in hexanes) to afford the lactol **22** (7.2 g) as a colourless oil in 86% yield. $R_f = 0{\cdot}53$ (1 : 1 ethyl acetate/hexanes).

A mixture of lactol **22** (5 g, 31·2 mmol), K_2CO_3 (13 g, 93·6 mmol) was heated to reflux. When the reflux initiated, dimethyl-1-diazo-2-oxopropylphosphonate **23** (20 g, 93·6 mmol) was added drop-wise over a period of 6 h using a syringe pump. The reaction mixture was cooled to room temperature and the stirring was continued for further 12 h. Filtered, solvent was evaporated, treated with water and then extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (22% EtOAc in hexanes) to afford the alcohol **24** (3·7 g) as a colourless oil in 76% yield. $R_f = 0{\cdot}5$ (1 : 1 ethyl acetate/hexanes); $[\alpha]^{25}_D = -35{\cdot}29$ ($c = 1{\cdot}36$, $CHCl_3$); IR (neat) 3306, 2937, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4·6 (*dd*, 1 H, $J = 7{\cdot}5$, 2·1 Hz, C<u>H</u>), 4·19 (*dt*, 1 H, $J = 7{\cdot}5$, 3·3 Hz, C<u>H</u>), 3·91 (*dd*, 1 H, $J = 3{\cdot}0$, 12·6 Hz, C<u>H</u> of CH_2), 3·69 (*dd*, 1 H, $J = 3{\cdot}6$, 12·6 Hz, C<u>H</u> of CH_2), 2·55 (*d*, 1 H, $J = 2{\cdot}1$ Hz, ≡C<u>H</u>), 1·51 (*s*, 3 H, C<u>H</u>$_3$), 1·44 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110·7, 82·0, 80·7, 74·9, 66·2, 60·7, 26·7, 26·1; LRMS (ES) $[M + Na]^+$ 179·1115; HRMS (ES) calcd. for $C_8H_{12}O_3Na$ *m/z* 179·0684, found *m/z* 179·0677.

2.1g *Tert-Butyl-(5-ethynyl-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-dimethyl-silane (**25**):* A solution of alcohol **24** (2·5 g, 19·23 mmol), imidazole (1·63 g, 24·03 mmol) and catalytic amount of DMAP in CH_2Cl_2 (50 mL) was treated with TBSCl (2·9 g, 19·23 mmol) at room temperature. After being stirred at room temperature for 2 h, the reaction mixture was treated with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (2% EtOAc in hexanes) to afford the silyl ether **25** (3·8 g) as a colourless oil in 88% yield.

$R_f = 0{\cdot}81$ (1 : 9 ethyl acetate/hexanes); $[\alpha]^{25}_D = -14{\cdot}52$ ($c = 1{\cdot}17$, $CHCl_3$); IR (neat) 3019, 2930, 2858, 2030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4·6 (*dd*, 1 H, $J = 7{\cdot}2$, 2·1 Hz, C<u>H</u>), 4·12 (*dt*, 1 H, $J = 7{\cdot}2$, 3·9 Hz, C<u>H</u>), 3·9 (*d*, 2 H, $J = 3{\cdot}9$ Hz, C<u>H</u>$_2$), 2·52 (*d*, 1 H, $J = 2{\cdot}1$ Hz, ≡C<u>H</u>), 1·49 (*s*, 3 H, C<u>H</u>$_3$), 1·41 (*s*, 3 H, C<u>H</u>$_3$), 0·90 (*s*, 9 H, 3 × C<u>H</u>$_3$), 0·08 (*s*, 6 H, 2 × C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110·7, 82·4, 81·4, 74·5, 67·1, 62·1, 27·0, 26·4, 26·0, 18·5, –5·2, –5·3; LRMS (ES) $[M + Na]^+$ 293·1760; HRMS (ES) calcd. for $C_{14}H_{26}O_3NaSi$ *m/z* 293·1549, found *m/z* 293·1547.

2.1h *Tert-Butyl-(5-ethynyl-2,2-dimethyl-[1,3]dioxolan-4-yl-methoxy)-dimethyl-silane (**26**):* A solution of alkyne **25** (3·74 g, 13·9 mmol) in THF (65 mL) was treated with ^nBuLi (11·3 mL, 18 mmol, 1.6 M in hexane) at –78°C and after being stirred for 30 min. the reaction mixture was treated with HMPA (4·83 mL, 27·8 mmol) at –78°C followed by MeI (1·7 mL, 27·8 mmol). The stirring was continued at the same temperature for 20 min. and then slowly warmed to room temperature. After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (2% EtOAc in hexanes) to afford the silyl ether **26** (3·76 g) in 96% yield as a colourless oil. $R_f = 0{\cdot}27$ (hexanes); $[\alpha]^{25}_D = -28{\cdot}85$ (c 1·04, $CHCl_3$); IR (neat) 2931, 2246, 1802, 1257 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4·55 (*dq*, 1 H, $J = 7{\cdot}8$, 2·1 Hz, C<u>H</u>), 4·01 (*dt*, 1 H, $J = 7{\cdot}2$, 3·9 Hz, C<u>H</u>), 3·77 (*dd*, 2 H, $J = 3{\cdot}9$, 2·1 Hz, C<u>H</u>$_2$), 1·86 (*d*, 3 H, $J = 2{\cdot}1$ Hz, C<u>H</u>$_3$), 1·48 (*s*, 3 H, C<u>H</u>$_3$), 1·39 (*s*, 3 H, C<u>H</u>$_3$), 0·91 (*s*, 9 H, 3 × C<u>H</u>$_3$), 0·08 (*s*, 6 H, 2 × C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ109·9, 83·0, 82·2, 76·0, 67·5, 62·0, 26·9, 26·6, 25·9, 18·4, 3·8; LRMS (ES) $[M + Na]^+$ 307·2350; HRMS (ES) calcd. for $C_{15}H_{28}O_3NaSi$ *m/z* 307·1705, found *m/z* 307·1692.

2.1i *(2,2-Dimethyl-5-prop-1-ynyl-[1,3]dioxolan-4-yl)-methanol (**20**):* A solution of silyl ether **26** (3·7 g, 13·02 mmol) in THF (75 mL) was treated with a solution of TBAF (5·11 g, 19·5 mmol) in THF (25 mL) at 0°C. After being stirred at 0°C for 15 min., the reaction mixture was allowed to stir at room temperature for 2 h. The reaction mixture was treated with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), con-

centrated and purified by silica gel chromatography (20% EtOAc in hexanes) to afford the alcohol **20** (2·05 g) in 93% yield as a colourless oil. R_f = 0·15 (2 : 8 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = –19·31 (*c* 1·45, $CHCl_3$); IR (neat) 3437, 2991, 2247, 1218 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4·55 (*dq*, 1 H, *J* = 7·8, 2·1 Hz, C<u>H</u>), 4·08 (*dt*, 1 H, *J* = 7·8, 3·0 Hz, C<u>H</u>), 3·9 (*dd*, 1 H, *J* = 3·0, 12 Hz, C<u>H</u> of CH_2), 3·67 (*dd*, 1 H, *J* = 3·0, 12 Hz, C<u>H</u> of CH_2), 2·09 (*br s*, 1 H, O<u>H</u>), 1·87 (*d*, 3 H, *J* = 2·1 Hz, C<u>H</u>$_3$), 1·5 (*s*, 3 H, C<u>H</u>$_3$), 1·45 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110·0, 83·4, 81·9, 75·4, 66·8, 61·0, 26·8, 26·4, 3·7; HRMS (ES) calcd. for $C_9H_{14}O_3Na$ *m/z* 193·0841, found *m/z* 193·0836.

2.1j *4-Iodomethyl-2,2-dimethyl-5-prop-1-ynyl-[1,3] dioxolane (27):* To a solution of alcohol **20** (0·540 g, 3·17 mmol) in pyridine (15 mL) was added *p*-TsCl (1·2 g, 6·4 mmol) at 0°C. The stirring was continued at the same temperature for 20 min and then at room temperature for 12 h. The reaction mixture was treated with water and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (15% EtOAc in hexanes) to afford the tosyl ether (0·89 g) as a colourless oil in 87% yield.

R_f = 0·34 (2 : 8 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = –52·884 (*c* 1·04, $CHCl_3$); IR (neat) 3024, 1455, 1373 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7·81(*d*, 2 H, *J* = 7·8, 2 × C<u>H</u>= of Ph), 7·36 (*d*, 2 H, *J* = 7·8, 2 × C<u>H</u>= of Ph), 4·44 (*dq*, 1 H, *J* = 9·0, 2·1 Hz, C<u>H</u>), 4·25-4·06 (*m*, 3 H, 1 × C<u>H</u> and C<u>H</u>$_2$), 2·5 (*s*, 3 H, C<u>H</u>$_3$), 1·84 (*d*, 3 H, *J* = 2·1 Hz, C<u>H</u>$_3$), 1·44 (*s*, 3 H, C<u>H</u>$_3$), 1·32 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145·1, 132·8, 129·9, 128·1, 110·9, 84·0, 79·1, 74·8, 67·8, 67·4, 26·7, 26·5, 21·7, 3·7· HRMS (ES) calcd. for $C_{16}H_{20}O_5SNa$ *m/z* 347·0929, found 347·0941.

A mixture of tosyl ether (0·84 g, 2·6 mmol) and NaI (1·36 g, 9·06 mmol) in ethyl methyl ketone (87 mL) was heated to reflux for 12 h. The solvent was evaporated, treated with water and extracted with ethyl acetate. The organic layer was washed with thio solution, water, brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (4% EtOAc in hexanes) to afford the iodo compound **27** (0·6 g) as a colourless oil in 83% yield. R_f = 0.4 (2 : 8 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = –48·17 (*c* 1·64, $CHCl_3$); IR (neat) 2990, 2922, 2250, 1455, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4·40 (*dq*, 1 H, *J* = 4·5, 1·8 Hz, C<u>H</u>), 3·92 (*dt*, 1 H, *J* = 10·5, 4·5 Hz, C<u>H</u>), 3·37 (*dd*, 1 H, *J* = 10·5, 5·1 Hz, C<u>H</u> of CH_2), 3·28 (*dd*, 1 H, *J* = 10·5, 5·1 Hz, C<u>H</u> of CH_2), 1·88 (*d*, 3 H, *J* = 1·8 Hz, C<u>H</u>$_3$), 1·49 (*s*, 3 H, C<u>H</u>$_3$), 1·46 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ110·7, 84·0, 80·4, 75·4, 71·4, 27·3, 26·8, 4·9, 3·8.

2.1k *3-(4S,5R)-2,2-Dimethyl-5-(prop-1-ynyl)-1,3-dioxolan-4-yl)propanenitrile (29):* To a solution of CH_3CN (0·133 mL, 2·55 mmol) in THF (3 mL) at –78°C was added ^nBuLi (1·01 mL, 1·1 M in hexane) drop wise. After stirring at the same temperature for 1 h, a solution of **27** (0·285 g, 1·02 mmol) in THF (1·3 mL) was added and continued the stirring for another 2 h. The reaction mixture was slowly warmed to room temperature and treated with saturated NH_4Cl solution. The reaction mixture was extracted with ether. The organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (4% EtOAc in hexanes) to afford the nitrile **29** (0·042 g) as colourless oil in 21% yield along with starting material **27** (0·104 g). R_f = 0·4 (1 : 19 ethyl acetate/hexanes); IR (neat) 2989, 2934, 2853, 2248, 1442, 1373, 1239, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4·22 (*dq*, 1 H, *J* = 8·0, 2·0 Hz, C<u>H</u>), 4·00 (*dt*, 1 H, *J* = 8·0, 3·6 Hz, C<u>H</u>), 2·57–2·49 (*m*, 2 H, C<u>H</u>$_2$), 2·11–2·02 (*m*, 1 H, C<u>H</u>), 1·92–1·83 (*m*, 1 H, C<u>H</u>), 1·88 (*d*, 3 H, *J* = 2·0 Hz, C<u>H</u>$_3$), 1·46 (*s*, 3 H, C<u>H</u>$_3$), 1·39 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 119·1, 110·1, 84·1, 78·5, 74·7, 70·5, 28·0, 27·1, 26·5, 14·1, 3·8; HRMS (ES) calcd. for $C_{11}H_{15}O_2NNa$ *m/z* 216·0998, found *m/z* 216·0998.

2.1l *3-(2,2-Dimethyl-5-prop-1-ynyl-[1,3]dioxolan-4-yl)-acrylic acid ethyl ester (30):* To a solution of oxalyl chloride (0·62 mL, 7·06 mmol) in CH_2Cl_2 (20 mL) was added DMSO (1·0 mL, 14·11 mmol) at –78°C and after being stirred at the same temperature for 10 min. a solution of alcohol **20** (1·0 g, 5·88 mmol) in CH_2Cl_2 (9 mL) was added drop wise and continuously stirred for 1 h. Finally triethylamine (4·3 mL, 31·0 mmol) was added and the reaction mixture was stirred at –78°C for 20 min. and then gradually warmed to room temperature. The reaction mixture was treated with water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and the crude product was used for further reaction without any purification. R_f = 0·31 (40% EtOAc in hexanes); IR (neat) 3020, 2250, 1736, 1383, 1217 cm^{-1}.

A solution of carboethoxymethylenetriphenyl phosphorane (2·95 g, 8·82 mmol) in acetonitrile

(28 mL) was treated with a solution of above aldehyde in acetonitrile (14 mL) at room temperature and the stirring was continued for 2 h. The solvent was evaporated and the resulting liquid was purified by column chromatography (4% EtOAc in hexanes) to afford the unsaturated ester **30** (0·83 g) as a colourless oil in 68% yield for two steps. R_f = 0·78 (3 : 7 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = –112·72 (*c* 1·1, $CHCl_3$); IR (neat) 2989·5, 1722, 1375, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6·91 (*dd*, 1 H, *J* = 15·6, 5·6 Hz, C<u>H</u>=), 6·19 (*dd*, 1 H, *J* = 15·6, 1·6, C<u>H</u>=), 4·49 (*dq*, 1 H, *J* = 8·0, 1·6 Hz, C<u>H</u>), 4·3 (*dq*, 1 H, *J* = 8·4, 2 Hz, C<u>H</u>), 4·22 (*q*, 2 H, *J* = 7·2 Hz, C<u>H</u>$_2$), 1·89 (*d*, 3 H, *J* = 1·9 Hz, C<u>H</u>$_3$), 1·50 (*s*, 3 H, C<u>H</u>$_3$), 1·42 (*s*, 3 H, C<u>H</u>$_3$), 1·31 (*t*, 3 H, *J* = 7·2, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165·9, 142·2, 123·4, 110·6, 84·3, 80·6, 74·0, 70·7, 60·7, 26·8, 26·7,14·3, 3·8; HRMS (ES) calcd. for $C_{13}H_{18}O_4Na$ *m/z* 261·1103, found *m/z* 261·1102.

2.1m *3-(2,2-Dimethyl-5-prop-1-ynyl-[1,3]dioxolan-4-yl)-propionic acid ethyl ester (**31**)*: A suspension of Cu_2Cl_2 (0·21 g, 2·14 mmol) and the ester **30** (0·68 g, 2·85 mmol) in THF (40 mL) and MeOH (17 mL) at –20°C was treated with $NaBH_4$ (0·65 g, 17·12 mmol) in portion-wise over a period of 10 min. The resultant black suspension was stirred for an additional 30 min at the same temperature. The black precipitate was filtered off and the filtrate was concentrated. The slurry was treated with saturated NH_4Cl solution and extracted with ether. The organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (4% EtOAc in hexanes) to afford the saturated ester **31** (0·55 g) in 80% yield. R_f = 0·55 (2 : 8 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = –14·63 (*c* 1·23, $CHCl_3$); IR (neat) 2987, 2935, 2250, 1732, 1455, 1372 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4·21 (*dq*, 1 H, *J* = 8·0, 2·4 Hz, C<u>H</u>), 4·15 (*q*, 2 H, *J* = 7·2 Hz, C<u>H</u>$_2$), 4·15 (*q*, 1 H, *J* = 6·8 Hz, C<u>H</u>), 2·57–2·42 (*m*, 2 H, C<u>H</u>$_2$), 2·04–2·01 (*m*, 1 H, C<u>H</u> of CH_2), 1·93–1·87 (*m*, 1 H, C<u>H</u> of CH_2), 1·86 (*d*, 3 H, *J* = 1·6 Hz, C<u>H</u>$_3$), 1·44 (*s*, 3 H, C<u>H</u>$_3$), 1·38 (*s*, 3 H, C<u>H</u>$_3$), 1·27 (*t*, 3 H, *J* = 7·2 Hz, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173·1, 109·6, 83·5, 80·5, 75·2, 70·7, 60·6, 30·5, 27·2, 26·5, 14·3, 3·8; HRMS (ES) calcd. for $C_{13}H_{20}O_4Na$ *m/z* 263·1259, found *m/z* 263·1252.

2.1n *5-(2,2-Dimethyl-5-prop-1-ynyl-[1,3]dioxolan-4-yl)-pent-1-en-3-ol (**32**)*: A solution of ester **31** (0·54 g, 2·25 mmol) in toluene (11 mL) was treated with DIBAL-H (2·25 mL, 1 M solution in toluene) at –78°C in drop wise over a period of 15 min. After being stirred at –78°C for 30 min the reaction mixture was treated with MeOH and then allowed to warm to room temperature. Saturated solution of potassium sodium L-tartrate tetrahydrate was added, stirred for 30 min and extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), concentrated and the crude product was used for further reaction without any purification. R_f = 0·43 (2 : 8 ethyl acetate/hexanes); IR (neat) 3019, 2933, 2730, 1723, 1381, 1372 cm^{-1}.

To a stirred solution of above aldehyde (0·44 g, 2·25 mmol) in THF (11 mL) was added vinyl magnesium bromide (4·5 mL, 1 M solution in THF) drop wise at –78°C, stirred for 1h at –78°C and then for 12 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution, extracted with ethyl acetate. The organic layer was washed with water, brine, dried (Na_2SO_4), concentrated and purified by silica gel chromatography (20% EtOAc in hexanes) to afford the alcohol **32** (0·33 g) as a colourless oil in 66% yield for two steps. R_f = 0·48 (3 : 7 ethyl acetate/hexanes); $[\alpha]^{25}_D$ = –29·92 (*c* 1·27, $CHCl_3$); IR (neat) 3446, 3016, 2253, 1381 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5·95–5·83 (*m*, 1 H, C<u>H</u>=), 5·26 (*ddd*, 1 H, *J* = 17·1, 3·3, 1·5 Hz, C<u>H</u> of CH_2=), 5·13 (*ddd*, 1 H, *J* = 10·2, 1·5, 1·5 Hz, C<u>H</u> of CH_2=), 4·76–4·71 (*m*, 1 H, C<u>H</u>O), 4·22–4·11 (*m*, 1 H, C<u>H</u>), 4·09–4·03 (*m*, 1 H, C<u>H</u>), 1·87 (*d*, *J* = 2·1 Hz, 3 H, C<u>H</u>$_3$), 1·52 (*s*, 3 H, C<u>H</u>$_3$), 1·34 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140·8, 114·8, 109·4, 83·3, 81·4, 75·4, 72·5, 70·9, 33·2, 28·02, 27·7, 27·1, 26·5, 3·8; HRMS (ES) calcd. for $C_{13}H_{20}O_3Na$ *m/z* 247·1310, found *m/z* 247·1315.

2.1o *5-(2,2-Dimethyl-5-prop-1-ynyl-[1,3]dioxolan-4-yl)-pent-1-en-3-one (**19**)*: A solution of allylic alcohol **32** (0·2 g, 0·89 mmol) in CH_2Cl_2 (20 mL) was treated with MnO_2 (1·55 g, 17·9 mmol) at room temperature and the stirring was continued for 12 h. The reaction mixture was filtered through *Celite* and concentrated. The crude product was purified by silica gel chromatography (8 : 22 ethyl acetate/hexanes) to afford the ketone **19** (0·14 g) as a colourless oil in 70% yield. R_f = 0·6 (20% EtOAc in hexanes); $[\alpha]^{20}_D$ = –17·577 (*c* 0·355, $CHCl_3$); IR (neat) 2988, 2925, 2250, 1703, 1684, 1238 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6·41–6·24 (*m*, 1 H, C<u>H</u>=), 6·35 (*d*, 1 H, *J* = 10·4 Hz, C<u>H</u>=), 5·86 (*d*, 1 H, *J* = 10·4 Hz, C<u>H</u>=), 4·21 (*d*, 1 H, *J* = 8 Hz, C<u>H</u>), 3·95 (*dt*, 1 H,

J = 8, 6 Hz, C<u>H</u>), 2·87–2·7 (*m*, 2 H, C<u>H</u>$_2$), 2·08–1·90 (*m*, 1 H, C<u>H</u> of CH$_2$), 1·86 (*d*, 3 H, J = 1·2 Hz, C<u>H</u>$_3$), 1·88–1·73 (*m*, 1 H, C<u>H</u> of C<u>H</u>$_2$), 1·45 (*s*, 3 H, C<u>H</u>$_3$), 1·39 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200·1, 136·5,128·4, 109·6, 83·6, 80·7, 70·9, 70·3, 35·6, 27·2, 26·6, 25·9, 3·8; HRMS (ES) calcd. for $C_{13}H_{18}O_3Na$ *m/z* 245·1154, found *m/z* 245·1148.

2.1p *5-[2,2-Dimethyl-5-(2-methyl-1-methylene-allyl)-[1,3]dioxo-lan-4-yl]-pent-1-en-3-one (**33**):* A solution of enynone **19** (0·047 g, 0·21 mmol) in toluene (8 mL) was purged with ethylene for 20 min. A solution of Grubbs' catalyst **17** (0·018 g, 0·021 mmol) in toluene (1 mL) was added and the stirring was continued at room temperature for 36 h under an atmosphere of ethylene. Then, dimethyl sulphoxide (0·16 mL, 2·25 mmol) was added to the reaction mixture and stirred for 12 h at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (25% EtOAc in hexanes) to afford the diene **33** (0·027 g) as a yellow oil along with 0·022 g of unreacted starting material. The yield of the reaction is 86% based on 53% conversion. R_f = 0·58 (2 : 8 ethyl acetate/hexanes); IR (neat) 2986, 1683, 1371, 1241, 1066 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6·34–6·22 (*m*, 1 H, C<u>H</u>=), 6·33 (*d*, 1 H, J = 10·4 Hz, C<u>H</u>=), 5·85 (*d*, 1 H, J = 10·4 Hz, C<u>H</u>=), 5·41 (*s*, 1 H, C<u>H</u>= of C<u>H</u>$_2$), 5·31 (*s*, 1 H, C<u>H</u>= of C<u>H</u>$_2$), 5·19 (*s*, 1 H, C<u>H</u>= of C<u>H</u>$_2$), 5·05 (*s*, 1 H, C<u>H</u>= of C<u>H</u>$_2$), 4·45 (*d*, 1 H, J = 8·4 Hz, C<u>H</u>), 3·8 (*dt*, 1 H, J = 8·4, 6 Hz, C<u>H</u>), 2·9–2·7 (*m*, 2 H, C<u>H</u>$_2$), 2·04–1·97 (*m*, 1 H, C<u>H</u> of C<u>H</u>$_2$), 1·94 (*s*, 3 H, C<u>H</u>$_3$), 1·82–1·71 (*m*, 1 H, C<u>H</u> of C<u>H</u>$_2$), 1·46 (*s*, 3 H, C<u>H</u>$_3$), 1·44 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200·2, 144·9, 141·7, 136·7, 128·4, 114·4, 114·1, 108·5, 80·9, 80·7, 36·2, 27·5, 27·2, 26·8, 22·3·; HRMS (ES) calcd. for $C_{15}H_{22}O_3Na$ *m/z* 273·1467, found *m/z* 273·1462.

2.1q *4,4,13-Trimethyl-3,5,-dioxa-tricyclo[8.3.1.0^{2,6}] tetradec-1(13)-en-9-one (**18**):* A solution of enyne **19** (0·1 g, 0·45 mmol) in toluene (18 mL) was purged with ethylene for 20 min. A solution of Grubbs' catalyst **17** (0·038 g, 0·045 mmol) in toluene (1 mL) was added and then heated at 80°C for 48 h under an atmosphere of ethylene. Then, dimethyl sulphoxide (0·16 mL, 2·25 mmol) was added to the reaction mixture and stirred for 12 h at room temperature. The solvent was evaporated and the crude product was purified by column chromatography (25% EtOAc in hexanes) to afford the diene **18** (0·07 g) as a white solid in 62% yield. R_f = 0·44 (2 : 8 ethyl acetate/hexanes); m.p. = 98–100°C; $[\alpha]^{25}_D$ = –14·52 (*c* 0·57, $CHCl_3$); IR (KBr) 3352, 2921, 1701, 1445 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4·14–4·05 (*m*, 2 H, 2 × C<u>H</u> of CH$_2$), 2·85 (*d*, 2 H, J = 10·4 Hz, C<u>H</u>$_2$), 2·6 (*dt*, 1 H, J = 11·6, 3·2 Hz, C<u>H</u>), 2·3–1·88 (*m*, 6 H, 3 × C<u>H</u>$_2$), 1·81 (*s*, 3 H, C<u>H</u>$_3$), 1·71–1·62 (*m*, 2 H, C<u>H</u>$_2$), 1·45 (*s*, 3 H, C<u>H</u>$_3$), 1·44 (*s*, 3 H, C<u>H</u>$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 213·2, 145·5, 123·5, 107·9, 78·8, 78·3, 49·4, 36·7, 29·1, 27·4, 27·1, 27·03, 26·4, 19·3, 18·9; LRMS (ES) $[M + Na]^+$ 273·2426; HRMS (ES) calcd. for $C_{15}H_{22}O_3Na$ *m/z* 273·1467, found *m/z* 273·1475.

3. Results and discussion

In connection to this issue of generating simpler analogues of taxol in relatively fewer steps and also in continuation of our interest in synthesis of complex natural products with significant biological activity, we began a research program to develop a simple strategy to achieve this objective. We believed that the best way of reducing the number of steps would be utilization of domino reactions, which are considered to be superior to step-wise procedures as several reactions can be combined in a single step, and consequently the synthesis can be shortened significantly.[10] Furthermore, domino reactions avoid the unnecessary isolations and purifications of intermediates in multistep transformations and reduce considerable amount of solvents required for the purification, which is hazardous to environment, especially, in bulk scale preparations. Among domino reactions, the domino enyne metathesis/intramolecular Diels–Alder reaction is particularly attractive because of its elegance in generating bicyclic ring system with defined stereochemistry.[11] As a part of our chiron approach[12] towards the synthesis of simpler analogues of biologically active natural products from carbohydrates, we have already described a synthetic route for the AB-ring of taxol without gem dimethyl group employing the cross enyne metathesis/intramolecular Diels–Alder reaction (IMDAR)[12b] and here, we present the full account of all our attempts directed toward the generation of functionalized taxol rings. From a retro-synthetic perspective (scheme 1), we envisaged that the 6, 8-fused bicyclic compound **6**, corresponding to BC-ring of taxol, could be obtained by opening the furanoside ring of ketal **7** which in turn could be obtained from the corresponding enyne **8** by a domino intramolecular

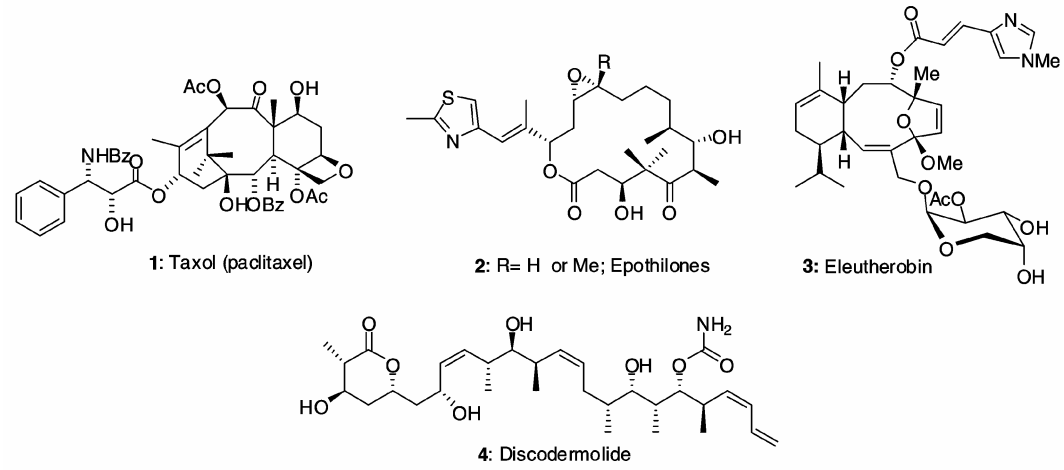
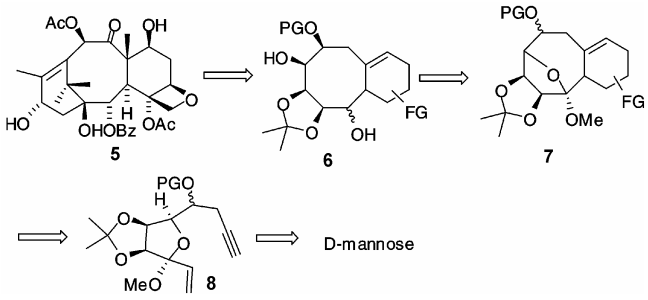


Figure 1. Microtubules stabilizing cytotoxic agents.



Scheme 1.

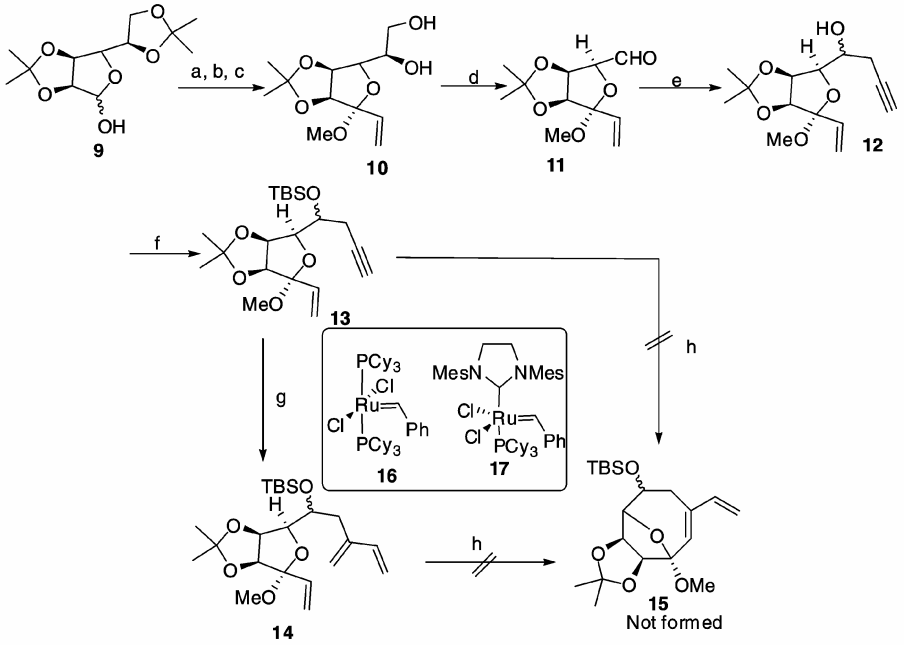
enyne metathesis/intermolecular Diels–Alder reaction and the requisite enyne **8** could be obtained from D-(+)-mannose through a sequence of reactions.

Accordingly, our synthesis (scheme 2) towards the highly oxygenated BC-ring of taxol **6** began with the D-(+)-mannose diacetonide **9** which was converted to the diol **10** using the protocol developed in our laboratory[13] and then, diol **10** was converted to aldehyde **11** using silica supported sodium periodide.[14] Treatment of aldehyde **11** under a Barbier type reaction[15] with propargyl bromide in the presence of zinc led to a diasteroemetic mixture alcohol **12** in 30 : 1 ratio as confirmed by ^{1}H NMR spectroscopy. Alcohol **12** was subsequently protected as its TBS ether to furnish **13**. Having the enyne in hand, we attempted the key intramolecular enyne metathesis reaction[16] to generate the B ring of taxol as a 1,3-diene which *in situ* could be reacted with appropriate dienophiles to afford the corresponding Diels–Alder adducts.

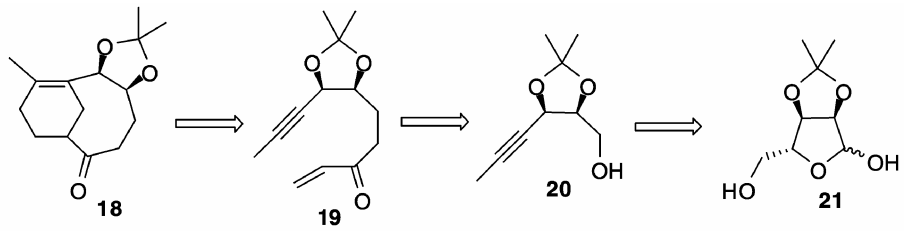
Unfortunately, our preliminary attempts with Grubbs' I generation catalyst **16** as well as more reactive Grubbs' II generation catalyst **17** in refluxing CH_2Cl_2 under an argon atmosphere did not lead to the desired product though starting material could be recovered. Nevertheless, when the enyne metathetic reaction was attempted with catalyst **17** in ethylene atmosphere, the cross enyne metathesis product **14** was obtained as a result of the reaction between the alkyne part and the ethylene gas which suggested that the alkene part is too inert to afford the intramolecular enyne metathesis product. Consequently, our further attempts of ring closing metathesis on **14** using the catalyst **17** were also not fruitful.

Although our attempts to generate the BC-ring of taxol using domino enyne metathesis/DAR reaction were not successful, it offered an essential clue that the intermolecular enyne metathesis reaction between ethylene and an alkyne could be employed as a key reaction in our synthesis.[17] Toward this end, we have devised a strategy based on domino cross enyne metathesis/intramolecular DAR for the synthesis of bicyclo[5.3.1] undecene as described in scheme 3. It is noteworthy that, bicyclo[5.3.1] undecene is an integral part of taxol and it corresponds to the AB-ring of the molecule without the gem dimethyl group.[18] Regardless of several excellent contributions from various groups for the synthesis of the AB-ring of taxol via an intramolecular Diels–Alder reaction (IMDAR),[19] the domino enyne cross-metathesis/IMDAR has not been explored, prior to our preliminary communication,[12b] for the construction of the corresponding 10-membered ring bridged by one carbon, which is bicyclo[5.3.1] undecene.

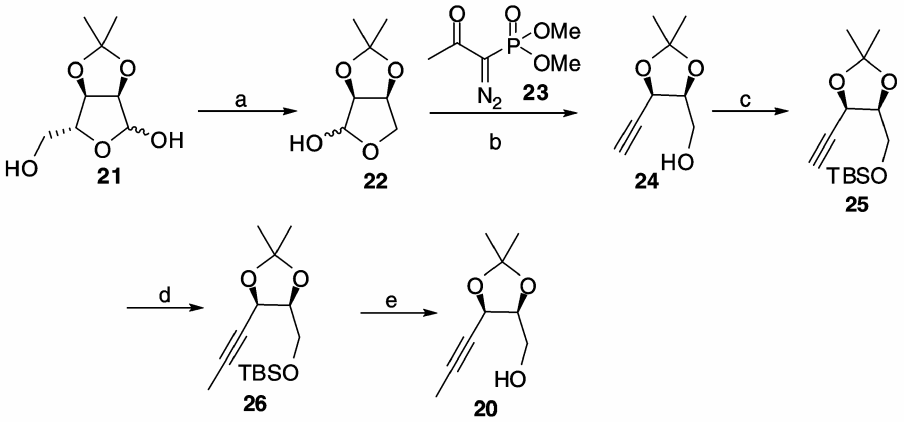
We envisaged that a domino enyne cross-metathesis/IMDAR could be an ideal key step for the construction of a bicyclo[5.3.1] undecene corresponding to the AB-ring of taxol but without the



Scheme 2. *Reagents and conditions:* (a) CH_2=CHMgBr, THF, 0°C to r.t., 12 h, 90%; (b) MnO_2, CH_2Cl_2, r.t., 6 h, 92%; (c) PPTS, MeOH, r.t., 12 h, 88%; (d) $NaIO_4$, silica, CH_2Cl_2, r.t., 2 h; (e) propargyl bromide, Zn, THF, r.t., 3 h, 67% over two steps; (f) TBSCl, Im, DMF, 50°C, 24 h, 83%; (g) **17**, ethylene, CH_2Cl_2, r.t., 3 h, 64%; (h) **17**, CH_2Cl_2, reflux.



Scheme 3.



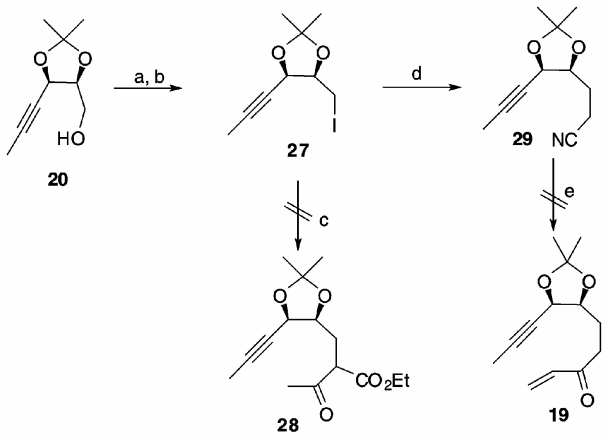
Scheme 4. *Reagents and conditions:* (a) $NaBH_4$, MeOH, 0°C, 2 h; then $NaIO_4$, H_2O, 3 h, 86%; (b) K_2CO_3, MeOH, reflux, 6 h, 76% (c) TBSCl, Im, cat. DMAP, CH_2Cl_2, r.t., 2 h, 78%; (d) ^{n}BuLi, CH_3I, HMPA, THF, –78°C to r.t., 12 h, 88%; (e) TBAF, THF, r.t., 2 h, 91%.

gem dimethyl group. From a retrosynthetic perspective (scheme 3), we considered the construction of **18** via domino cross-enyne metathesis/IMDA reaction of enyne **19**. This acyclic ketone **19** could, in turn, be obtained from the alkynol **20**. The alcohol **20** could then be derived from D-(+)-ribose monoacetonide **21** in a few steps. Our synthetic sequence (scheme 4) started with the known lactol **22**,[20] which was smoothly converted into the alkyne **24** by following the Ohira–Bestmann protocol in refluxing methanol in 76% yield.[21] The primary alcohol **24** was then protected as its TBS ether **25** before treatment with ^{n}BuLi and MeI to afford **26** in excellent yield. Removal of the TBS group was then easily achieved with TBAF to afford the alcohol **20** in 91% yield.

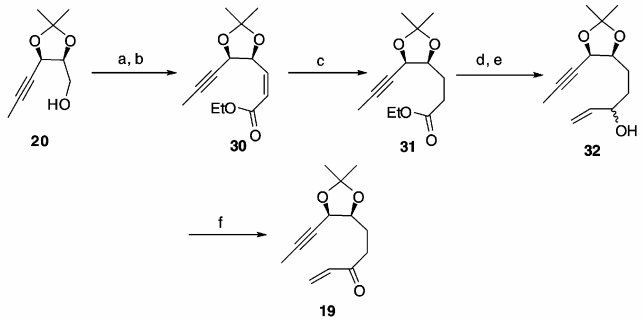
After the successful synthesis of alcohol **20**, our next goal was to extend two more carbons on the right hand side of this molecule to afford **19**. We envisaged that the alcohol **20** could be converted to the corresponding iodo compound **27**, which on reaction with the ethylacetoacetate in the presence of base should afford **28** (scheme 5). Decarboxylation followed by a Mannich reaction[22] of **28** should provide **19**, the precursor for the domino reaction in relatively less steps. Towards this end, the alcohol **20** was converted to the corresponding tosylate which on reaction with NaI in refluxing ethylmethyl ketone afforded the iodo compound **27**. But unfortunately, our attempts to synthesize **28** from **27** were unsuccessful under a variety of reaction conditions utilizing different bases, such as NaH, NaOEt and KO^{t}Bu.

Puzzled with the failure of the alkylation reaction, we decided to replace ethylacetoacetate with acetonitrile and effect the alkylation using LDA. Accordingly, the iodo compound **27** was treated with acetonitrile in the presence of LDA[23a] to afford the nitrile **29** in 11% yield along with unreacted starting material. When excess of LDA was used to improve the conversion of product, dialkylation product was observed as the predominant product. On the other hand, replacement of LDA with ^{n}BuLi improved the yield of reaction to 21% along with unreacted starting material.[23b] However, the subsequent Grignard reaction which would have furnished the ketone **19** in a single step was unsuccessful despite our repeated attempts and the starting material was recovered as unchanged.

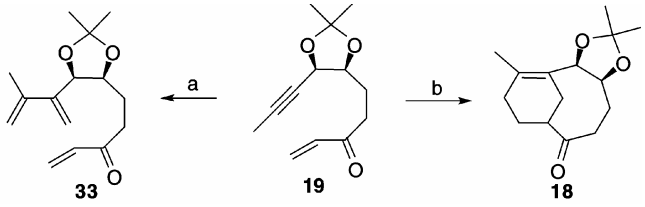
In an effort to find an alternative route, we modified our strategy to synthesize **19** as delineated in the scheme 6. We anticipated that the alcohol could be converted to α,β-unsaturated ester **30**, which in turn could be reduced to give the saturated ester **31** thereby providing the desired extension of two carbon atoms. Accordingly, we started this approach with the oxidation of alcohol **20**, under Swern conditions to provide an aldehyde, which was subsequently subjected to Wittig reaction to afford **30** in 60% yield over two steps (scheme 6). Our next task was to reduce the double bond of enone **30** selectively in the presence of the alkyne. Unfortunately, conventional reduction methods such as Mg/MeOH,[24] $NiCl_2/NaBH_4$,[25] copper(I) hydride cluster $[(Ph_3P)CuH]_6$[26] and CuI/LAH[27] did not yield the desired product. Finally, we were relieved to find that Cu_2Cl_2 (0·75 equiv)/$NaBH_4$ (6 equiv) effectively re-



Scheme 5. *Reagents and conditions:* (a) TsCl, Py, cat. DMAP, 12 h, 87%; (b) NaI, EMK, reflux, 12 h, 83%; (c) ethylacetoacetate, base; (d) CH_3CN, ^{n}BuLi, THF, –78°C, 1·5 h, 21%; (e) CH_2=CHMgBr, ether, –78°C to r.t., 12 h.



Scheme 6. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78°C, 1 h; (b) carboethoxymethylenetriphenylphosph-orrane, CH_3CN, r.t., 12 h, 68%; (c) Cu_2Cl_2, $NaBH_4$, THF, MeOH, –20°C, 30 min, 80%; (d) DIBAL-H, toluene, –78°C, 30 min, 84%; (e) CH_2=CHMgBr, THF, –78°C to r.t., 12 h, 53%; (f) MnO_2, CH_2Cl_2, r.t., 12 h, 67%.



Scheme 7. *Reagents and conditions:* (a) **17** (10 mol%), ethylene, toluene, r.t., 36 h, 86% based on 53% conversion; (b) **17** (10 mol%), ethylene, toluene, 80°C, 24 h, 62%.

duced this unsaturated ester selectively at –20°C to provide **31** in 80% yield.[28] Subsequently, **31** was treated with DIBAL-H to afford the aldehyde, which on treatment with vinyl magnesium bromide afforded a diastereomeric mixture of allylic alcohols **32** in 66% yield for two steps. The oxidation of allylic alcohol **32** with MnO_2 afforded the ketone **19** in 67% yield. The alkenynone **19** was found to be very unstable and polymerized quite rapidly even in the refrigerator.

Synthesis of **19** set the stage for the domino cross enyne metathesis/IMDA reaction. When we carried out this reaction under 1 atm. of ethylene in the presence of **17** in toluene at room temperature for 36 h (scheme 7), we isolated the trienone **33** in 86% yield based on 53% conversion.[29] We were hopeful that a domino cross enyne/IMDA reaction could be achieved if we performed the reaction at higher temperature, and indeed at 80°C, we were delighted to see a smooth domino enyne metathesis/IMDA reaction of enyne **19** to afford a single diastereomer of the bicyclo[5.3.1] undecanone **18** which corresponds to the AB-ring skeleton of taxol without the gem dimethyl group in 62% yield.

4. Conclusions

In conclusion, our preliminary efforts to generate the BC-ring of taxol using enyne metathesis/intermolecular DAR led to the formation of only a triene which was formed by an intermolecular enyne metathesis with ethylene. However, we could successfully develop a simple and straightforward tandem enyne cross-metathesis/IMDA reaction strategy for the construction of bicyclo[5.3.1] undecene system which is the structural sub-unit that constitutes AB-ring system of taxol without the gem dimethyl group. Efforts are underway in our laboratory to extend this strategy to synthesize the core structure and finally to synthesize taxol.

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References

1. Wani M C, Taylor H L, Wall M E, Coggon P and McPhail A T 1971 *J. Am. Chem. Soc.* **93** 2325
2. For review on taxol, see: Kingston D G I 2001 *Chem. Commun*. 867
3. (a) Holton R A, Somoza C, Kim H B, Liang F, Biediger R J, Boatman P D, Shindo M, Smith C C, Kim S, Nadizadeh H, Suzuki Y, Tao C, Vu P, Tang S, Zhang P, Murthi K K, Gentile L N and Liu J H 1994 *J. Am. Chem. Soc.* **116** 1597; (b) Holton R Somoza A C, Kim H B, Liang F, Biediger R J, Boatman P D, Shindo M, Smith C C, Kim S, Nadizadeh H, Suzuki Y, Tao C, Vu P, Tang S, Zhang P, Murthi K K, Gentile L N and Liu J H 1994 *J. Am. Chem. Soc.* **116** 1599
4. (a) Nicolaou K C, Nantermet P G, Ueno H, Guy R K, Couladouros E A and Sorensen E J 1995 *J. Am. Chem. Soc.* **117** 624; (b) Nicolaou K C, Liu J-J, Yang Z, Ueno H, Sorensen E J, Claiborne C F, Guy R K, Hwang C-K, Nakada M and Sorensen E J 1995 *J. Am. Chem. Soc.* **117** 634; (c) Nicolaou K C, Yang Z, Liu J-J, Nantermet P G, Claiborne C F, Renaud J, Guy R K and Shibayama K 1995 *J. Am. Chem. Soc.* **117** 645; (d) Nicolaou K C, Ueno H, Liu J-J, Nantermet P G, Yang Z, Renaud J, Paulvannan K and Chadha R J 1995 *J. Am. Chem. Soc.* **117** 653
5. Danishefsky S J, Masters J J, Young W B, Link J T, Snyder L B, Magee T V, Jung D K, Isaacs R C A, Bornmann W G, Alaimo C A, Coburn C A and DiGrandi M J 1996 *J. Am. Chem. Soc.* **118** 2843
6. (a) Wender P A, Badham N F, Conway S P, Floreancig P E, Glass T E, Granicher C, Houze J B, Janichen J, Lee D, Marquess D G, McGrane P L, Meng W, Mucciaro T P, Muhlebach M, Natchus M G, Paulsen H, Rawlins D B, Satkofsky J, Shuker A J, Sutton J C, Taylor R E and Tommoka K 1997 *J. Am. Chem. Soc.* **119** 2755; (b) Wender P A, Badham N F, Conway S P, Floreancig P E, Glass T E, Houze J B, Krauss N E, Lee D, Marquess D G, McGrane P L, Meng W, Natchus M G, Shuker A J, Sutton J C and Taylor R E 1997 *J. Am. Chem. Soc.* **119** 2757
7. (a) Hara R, Kawahara S, Nishimori T, Kashima H, Nakamura N, Morihira K and Kuwajima I 1998 *J. Am. Chem. Soc.* **120** 12980; (b) Kusama H, Hara R, Kawahara S, Nishimori T, Kashima H, Nakamura N, Morihira K and Kuwajima I 2000 *J. Am. Chem. Soc.* **122** 3811
8. Mukaiyama T, Shiina I, Iwadare H, Saitoh M, Nishimura T, Ohkawa N, Sakoh H, Nishimura K, Tani Y I, Hasegawa M, Yamada K and Saitoh K 1999 *Chem. Eur. J.* **5** 121

9. Holton R A, Biediger R J and Boatman P D 1995 In *Taxol®: Science and Applications* (ed.) M Suffness (FL: CRC Press) pp 97–122
10. For reviews on domino reactions, see: (a) Posner G H 1986 *Chem Rev*. **86** 83l; (b) Ho T-L 1992 *Tandem organic reactions* (New York: Wiley); (c) Tietze L F and Beifuss U 1993 *Angew. Chem., Int. Ed. Engl.* **32** 131; (d) Fukumoto K 1994 *J. Synth. Org. Chem. Jpn.* **52** 2; (e) Bunce R A 1995 *Tetrahedron* **51** 13103; (f) Tietze L F 1996 *Chem Rev.* **96** 115; (g) Parsons P J, Penkett C S and Shell A J 1996 *Chem. Rev.* **96** 195; (h) Tietze L F and Rackelmann N 2004 *Pure Appl. Chem.* **76** 1967; (i) Pellissier H 2006 *Tetrahedron* **62** 1619; (j) Tietze L F, Brasche G and Gericke K M 1992 *Domino reactions in organic synthesis* (Wiley-VCH)
11. (a) Schurer S C and Blechert S 1999 *Tetrahedron Lett*. **40** 1877; (b) Schurer S C and Blechert S 1999 *Chem. Commun.* 1203; (c) Kotha S, Halder S and Brahmachari E 2002 *Tetrahedron* **58** 9203
12. (a) Kaliappan K P and Ravikumar V 2005 *Org. Biomol. Chem*. **3** 848; (b) Kaliappan K P and Ravikumar V and Pujari S A 2006 *Tetrahedron Lett*. **47** 981
13. Kaliappan K P, Das P and Kumar N 2005 *Tetrahedron Lett*. **46** 3037
14. Zhong Y-L and Shing T K M 1997 *J. Org. Chem*. **62** 2622
15. Pakulski S and Zamojsky A 1997 *Tetrahedron* **53** 2653
16. For reviews on enyne metathesis, see: (a) Mori M 1998 In *Enyne metathesis* in *Top. Organomet. Chem.* (ed.) A Furstner (Berlin Heidelberg: Springer) pp 133; (b) Poulsen C S and Madsen R 2003 *Synthesis* 1; (c) Diver S T and Giessert A J 2004 *Chem. Rev.* **104** 1317
17. For domino ethylene cross-enyne metathesis/IMDA reaction, see: Nishiguchi N, Kinoshita A and Mori M 2000 *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **42** 739, CA No. 134:340567; For domino cross-enyne metathesis/IMDA reaction, see: Mix S and Blechert S 2005 *Org. Lett.* **7** 2015
18. (a) For review, see: Mehta G and Singh V 1999 *Chem. Rev.* **99** 881; (b) Oh J, Choi J-R and Cha J K 1992 *J. Org. Chem*. **57** 6664; (c) Kraus G A and Zheng D 1993 *Synlett* 71; (d) Mukaiyama T, Shiina I, Kimura K, Akiyama Y and Iwadare H 1995 *Chem. Lett.* 229; (e) Shiina I, Iwadare H, Saitoh M, Ohkawa N, Nishimura T and Mukaiyama T 1995 *Chem. Lett.* 781; (f) Crich D and Natarajan S 1995 *Chem. Commun.* 85; (g) Banwell M G, Darmos P, McLeod M D and Hockless D C R 1998 *Synlett* 897; (h) Wenz M, Grobach D, Beitzel M and Blechert S 1999 *Synthesis* **4** 607; (i) Shimada Y, Nakamura M, Suzuka T, Matsui J, Tatsumi T, Tsutsumi K, Morimoto T, Kurosawa H and Kaiuch K 2003 *Tetrahedron Lett.* **44** 14013
19. For an excellent review on IMDA, see: Bear B R, Sparks S M and Shea K J 2001 *Angew. Chem., Int. Ed. Engl.* **40** 820; Also see: (a) Shea K J and Davis P D 1983 *Angew. Chem. Int. Ed. Engl*. **22** 419; (b) Shea K J and Gilman J 1985 *J. Am. Chem. Soc*. **107** 4791; (c) Bonnert R V and Jenkins P R 1987 *J. Chem. Soc. Chem. Commun.* 1540; (d) Shea K J and Haffner C D 1988 *Tetrahedron Lett.* **29** 1367; (e) Yadav J S and Ravishankar R 1991 *Tetrahedron Lett*. **32** 2629; (f) Phillips A J, Morris J C and Abell A D 2000 *Tetrahedron Lett*. **41** 2723; (g) Jackson R W and Shea K J 1994 *Tetrahedron Lett.* **35** 1317; (h) Forgione P, Wilson P D, Yap G P A and Fallis A G 2000 *Synthesis* 921; (i) Winkler J D, Kim S H and Kim H S 1995 *Tetrahedron Lett.* **36** 687; (j) Winkler J D, Kim H S, Kim S H, Ando K and Houk K N 1997 *J. Org. Chem.* **62** 2957; (k) Winkler J D, Holland J M and Peters D A 1996 *J. Org. Chem.* **61** 9074; (l) Vuzquez A and Williams R M 2000 *J. Org. Chem.* **65** 7865
20. (a) Paquette L A and Bailey S 1995 *J. Org. Chem.* **60** 7849; (b) Krishna U M, Srikanth G S C, Trivedi G K and Deodhar K D 2003 *Synlett* 2383
21. (a) Ohira S 1989 *Synth. Commun.* **19** 561; (b) Muller S, Liepold B, Roth G J and Bestmann H J 1996 *Synlett* 521
22. Grast J-L 1978 *Tetrahedron Lett*. **19** 2955
23. (a) Larcheveque M, Perrior P and Petit Y 1983 *Synthesis* 297; (b) Taber D F and Kong S 1997 *J. Org. Chem.* **62** 8575
24. (a) Dominquez C, Csaky A G and Plumet J 1991 *Tetrahedron Lett*. **32** 4183; (b) Youn I K, Yon G H and Pak C S 1986 *Tetrahedron Lett.* **26** 2409
25. (a) Saksena A K, Lovey R G, Girijavallabhan V M, Ganguly A K and McPhail A T 1986 *J. Org. Chem.* **51** 5024; (b) Stien D and Gastaldi S 2004 *J. Org. Chem.* **69** 4464; (c) Shin Y, Fournier J H, Balachandran R, Madiraju C, Raccor B S, Zhu G, Edler M C, Hamel E, Day B W and Curran D P 2005 *Org. Lett.* **7** 2873
26. (a) Brestensky D M, Huseland D E, McGettigan C and Stryker J M 1988 *Tetrahedron Lett*. **29** 3749; (b) Mahoney W S, Brestensky D M and Stryker J M 1988 *J. Am. Chem. Soc.* **110** 291
27. Ashby E C, Lin J J and Kovar R 1976 *J. Org. Chem.* **41** 1939
28. Narisada M, Horibe I, Watanabe F and Takeda K 1989 *J. Org. Chem.* **54** 5308
29. Kinoshita A, Sakakibara N and Mori M 1999 *Tetrahedron* **55** 8155