Pergamon

Tetrahedron 55 (1999) 5185–5194

TETRAHEDRON

Diels-Alder Approach Towards the Stereocontrolled Construction of a Taxol® C Ring Fragment

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Received 2 September 1998; revised 1 February 1999; accepted 18 February 1999

Abstract : An elegant stereocontrolled synthesis of a highly functionalized C ring fragment of taxol® is described. The route utilises a new Diels-Alder reaction followed by regioselective opening of anhydride, reductive dechlorination, Baeyer-Villiger oxidation of norbornenone system and stereodirected hydroboration using thexylborane as the key steps.

INTRODUCTION

Taxol® (paclitaxel) **1**, the novel polyoxygenated diterpenoid and a potent antitumor agent isolated from the bark of Western yew *Taxus brevifolia*,[1] has become one of the most important members in a new class of chemotherapeutic agents. It has recently been approved by FDA[2] for the treatment of refractive ovarian cancer and metastatic breast cancer and clinical trials are ongoing against a variety of other cancer disease types including nonsmall cell lung cancer (nsclc), head and neck cancer, glioblastoma and oesophageal cancer. Taxol® affects the tubulin-microtubule equilibrium and promotes the assembly of tubulin into heat- and calcium- stable microtubules,[3] and this presumably prevents cellular division and facilitates cell death. These properties of taxol® and also its intricate molecular architecture have stimulated legions of synthetic organic chemists[4] towards the synthesis of paclitaxel and its analogues. As a result of extensive research on taxol® during the past two decades, a few groups[5] have accomplished the total synthesis of taxol®. Despite this success, many factors remain to be investigated for synthesizing simpler analogues with better therapeutic profiles. In continuation of our programme on taxol® and its analogues,[6] we report herein an elegant stereocontrolled synthesis of a densely functionalized C ring fragment[7] of paclitaxel utilizing a new Diels-Alder reaction.

IICT Communication No. 4128

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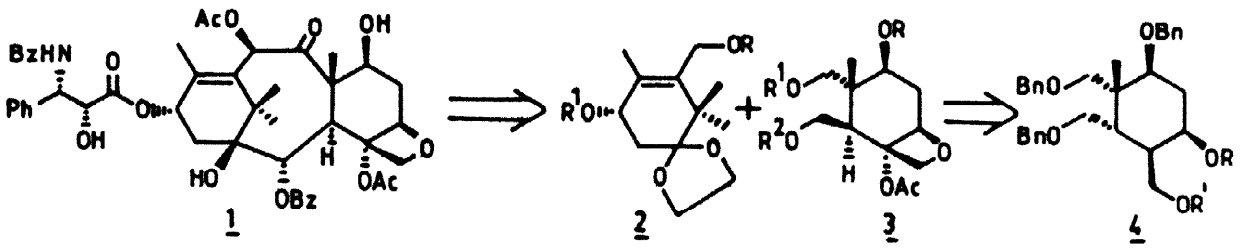
PII: S0040-4020(99)00165-9

RESULTS AND DISCUSSION

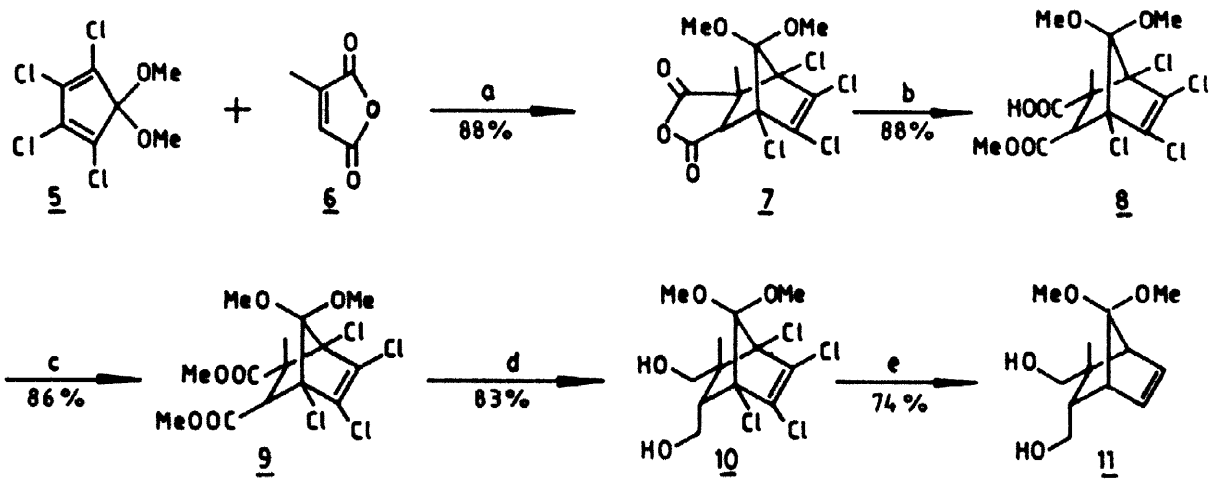
Our retrosynthetic analysis was based on a convergent strategy which revealed that the A- ring building block **2** can be appended to CD substructure **3** *via* a suitable coupling procedure (**Scheme-1**). Intermediate **3**, in turn, can be obtained from the key retron **4** by an oxetane annulation process, reported earlier by our group.[6c]

Scheme - 1



Diels-Alder reaction between 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene **5** (easily obtained from commercially available hexachlorocyclopentadiene[8]) and citraconic anhydride **6** in *ortho*- dichlorobenzene under refluxing conditions afforded cycloadduct **7** (**Scheme-2**).

Scheme - 2

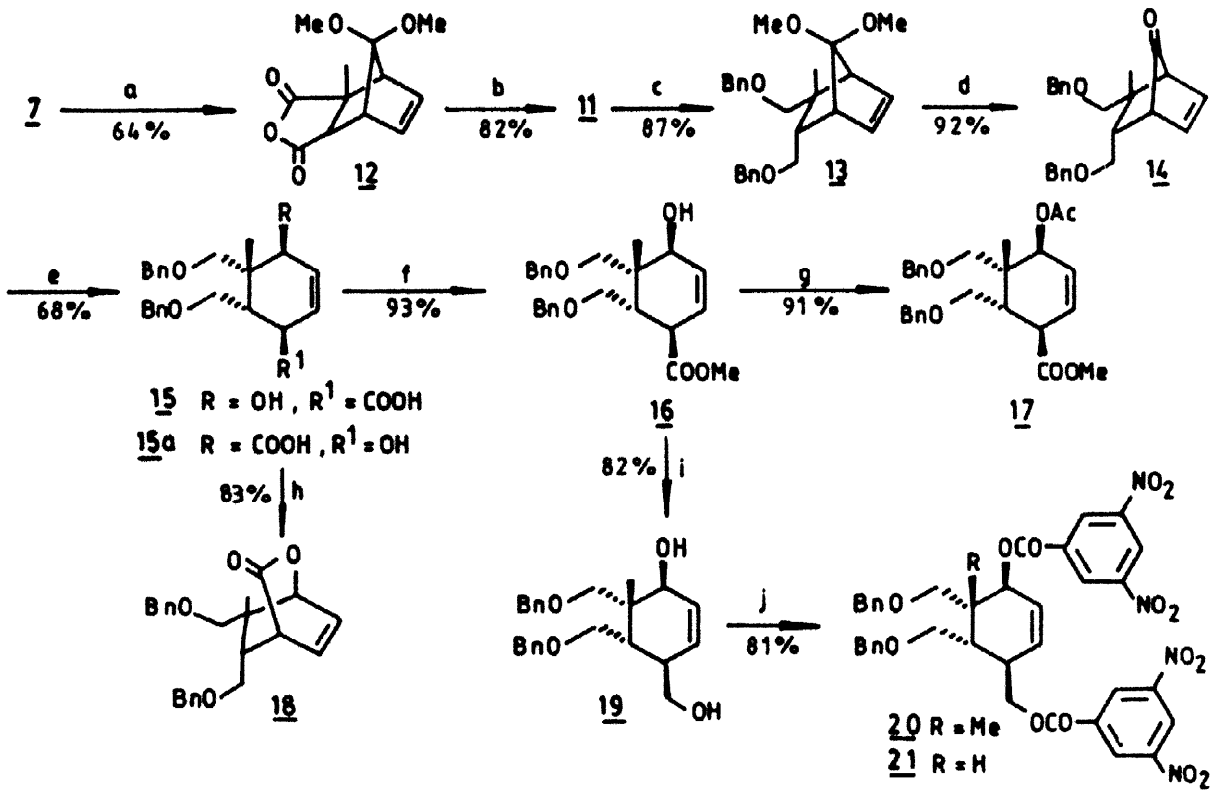


Reagents and conditions: a) 1,2-dichlorobenzene, reflux, 72 h, 88%, b) MeOH, dry HCl, reflux, 88%, c) Me_2SO_4, K_2CO_3, DMF, rt, 86%, d) LAH, ether, reflux, 83%, e) Na, liq. NH_3, -33 °C, THF-EtOH, 74%.

Anhydride **7** on treatment with dry methanolic HCl solution either at room temperature or under refluxing conditions, contrary to our expectation, furnished half ester **8**. Compound **8** in its ^{13}C NMR spectrum showed only 13 lines which proved the 100% regioselectivity in the half esterification process and also gave evidence for the exclusive *endo* selectivity of the Diels-Alder reaction. Treatment of **8** with K_2CO_3/Me_2SO_4 in DMF produced diester **9**. The ester group in **9** was reduced with $LiAlH_4$ in refluxing ether to diol **10** which was then subjected to reductive dechlorination[9] using sodium in liquid ammonia to afford compound **11**.

Then, a shorter route for the conversion of **7** into **11** was developed. Diels-Alder adduct **7** was first dechlorinated to anhydride **12** which on treatment with $LiAlH_4$ in THF furnished the same diol **11** (**Scheme-3**). Diol **11** was protected as its dibenzyl ether **13** which on deketalisation with PTSA in dry acetone generated the bridged keto compound **14**. Though norbornenones exhibit a great propensity to form a hydrate upon exposure to moisture, the diagnostic carbonyl absorption at 1780 cm^{-1} in the IR spectrum confirmed the presence of a bridged keto functionality. Compound **14** was subjected to Baeyer-Villiger oxidation[10] using alkaline H_2O_2 in MeOH to get two isomers **15** and **15a** in a 9:1 ratio. The major isomer **15** was separated and treated with an ethereal solution of diazomethane to give hydroxy ester **16**.

Scheme - 3



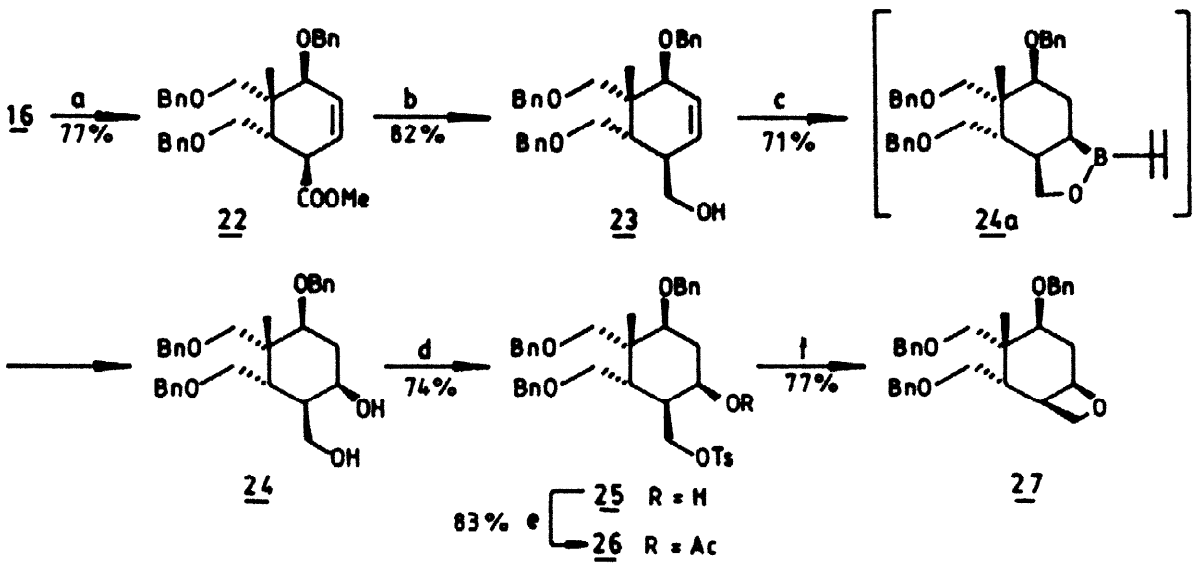
Reagents and conditions: a) Na, liq. NH_3, -33 °C, THF-EtOH, 64%, b) LAH, THF, rt, 82%, c) NaH, BnBr, $^nBu_4N^+I^-$ (cat), THF, 87%, d) PTSA (cat), dry acetone, rt, 92%, e) aq. NaOH, 30% H_2O_2, MeOH, 68%, f) CH_2N_2 in ether, 0 °C, 93%, g) Ac_2O, Et_3N, DMAP (cat), DCM, 91%, h) Ac_2O, NaOAc, benzene, reflux, 83%, i) LAH, THF, 82%, j) 3,5-dinitrobenzoyl chloride, DMAP, DCM, 81%.

The syn orientation of the hydroxyl and carboxylic acid functionality in **15** was confirmed by making bridged lactone **18** upon treating compound **15** with Ac_2O and NaOAc in refluxing benzene.[11] The position of the methyl group was confirmed by decoupling experiments of acetyl derivative **17** and lactone **18**. Compound **16** was treated with $LiAlH_4$ to give diol **19** which was diesterified as its 3,5-dinitrobenzoate derivative **20**. Following the same sequence of reactions, the Diels-Alder adduct of **5** and maleic anhydride[12] was manipulated in several steps to give the 3,5-dinitrobenzoate derivative **21**. Now by comparing the splitting pattern and coupling constant (J) values of the allylic proton adjacent to 3,5-dinitrobenzoate group in **20** and **21**, it was

concluded that the methyl group was in the desired position. In compound **20**, the said proton resonated at δ 5.62 as a doublet with J value of 1.8 Hz whereas in compound **21**, the corresponding proton resonated at δ 5.72 as a double doublet with J values of 1.8 Hz and 7.2 Hz.

After confirming the position of the methyl group, compound **16** was protected as its benzyl ether derivative **22** using benzyl trichloroacetimidate[13] and a catalytic amount of camphorsulfonic acid (**Scheme-4**).

Scheme-4



Reagents and conditions: a) benzyl trichloroacetimidate, CSA (cat), DCM-cyclohexane (1:2), rt, 77%, b) LAH, THF, 82%, c) thexylborane, THF, 0 °C to rt, 6 h, then 30% H_2O_2, aq. NaOH, 71%, d) TsCl (1.1 eq.), Py, DMAP (cat), DCM, 74%, e) Ac_2O, Et_3N, DMAP (cat), DCM, 83%, f) NaH, THF, rt, 77%.

Compound **22** was treated with $LiAlH_4$ to give alcohol **23** which was subjected to hydroboration using thexylborane[14] in THF to give the desired key retron **24**. The secondary hydroxyl group in compound **24** was introduced in a stereo- and regio- controlled manner due to the formation of intermediate borane chelate **24a**. The position and the relative stereochemistry of diol **24** was confirmed by making the oxetane ring in **27**. For this, the primary hydroxyl group was tosylated to give compound **25** which on treatment with NaH in THF generated oxetane **27**. Compound **25** was also characterised by making its acetyl derivative **26**.

In summary, we have demonstrated a facile stereocontrolled synthesis of a densely functionalized C-ring fragment of taxol®, specially to introduce a methyl group at the BC ring juncture of taxol®. Coupling between the C-ring and A-ring fragments, followed by oxetane annulation and further elaboration towards taxol® is currently being investigated.

EXPERIMENTAL

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. Moisture and air sensitive reactions were carried out under nitrogen atmosphere using dry solvents, prepared by standard procedures. IR spectra were recorded either as a KBr wafer or neat on a Perkin-Elmer infrared 683 spectrophotometer with NaCl optics. ^1H NMR and ^{13}C NMR spectra were recorded on Varian Unity 400 or Varian Gemini 200

spectrometers. The samples were dissolved in $CDCl_3$, using tetramethylsilane as the internal standard and spectra are given in the δ scale. Mass measurements were carried out on a CEC-21-110B double focussing mass spectrometer operating at 70 eV and are given in the mass units (m/z). CHN analyses were recorded on a Vario EL analyzer. TLC was performed on 0.25 mm E.Merck precoated silica plates (60F-254). All the products were purified by column chromatography on silica gel (100-200 mesh). All the compounds were characterised mainly based on their ^1H NMR spectra.

1,7,8,9-Tetrachloro-10,10-dimethoxy-2-methyl-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-ene-2,6-*endo*, *endo*-3,5-dione (7):

A solution containing **5** (26.4 g, 0.1 mol) and **6** (11.2 g, 0.1 mol) in *ortho*-dichlorobenzene (150 mL) was refluxed for 72 h. After cooling, hexane (300 mL) was added and the mixture was kept in the freezer. The crystallised solid was filtered and washed with hexane to get pale yellow crystals of **7** (33.1 g, 88% yield). A small amount of **7** was recrystallised from benzene/chloroform (10:1), mp 168-169 °C; ^1H NMR: δ 1.76 (s, 3H), 3.52 (s, 1H), 3.60 (s, 3H), 3.66 (s, 3H); IR : 2945, 1840, 1760 cm^{-1}; EIMS: m/z 344, 339, 267, 221; FABMS: 375 (M+1), 339; HRMS : calcd. for $C_{12}H_{11}Cl_4O_5$ 374.9361, found 374.9365

1,4,5,6-Tetrachloro-7,7-dimethoxy-2-methylbicyclo[2.2.1]hept-5-ene-2,3-*endo,endo*-dicarboxylic acid 3-methyl ester (8):

Compound **7** (4 g, 10.6 mmol) was dissolved in MeOH (40 mL), presaturated with dry HCl gas. The mixture was refluxed for 12 h. Methanol was distilled off and the solid residue was crystallised from benzene to get colourless crystals of **8** (3.81 g, 88% yield), mp 154-155 °C (dec.); ^1H NMR: δ 1.84 (s, 3H), 3.50 (s, 1H), 3.52 (s, 3H), 3.60 (s, 3H), 3.65 (s, 3H); ^{13}C NMR: δ 21.51, 51.79, 52.08, 52.96, 59.96, 60.26, 74.71, 79.07, 112.61, 130.51, 130.75, 168.66, 175.63; IR: 3500-2500 (br), 1755, 1702 cm^{-1}; FABMS: m/z 407 ((M+1), 371; Anal. calcd. for $C_{13}H_{14}Cl_4O_6$: C 38.26, H 3.46; found C 38.12, H 3.52

Dimethyl 1,4,5,6-tetrachloro-7,7-dimethoxy-2-methylbicyclo[2.2.1]hept-5-ene-2,3-*endo,endo*-dicarboxylate (9):

To a solution of **8** (3.8 g, 9.3 mmol) in dry DMF (25 mL), anhydrous K_2CO_3 (3.85 g, 27.9 mmol) was added and then at 0 °C Me_2SO_4 (1.1 mL, 11.5 mmol) was introduced dropwise. After stirring for 4 h at room temperature, the solid was filtered off and the filtrate was treated with ice-cold water and extracted with ether (3x50 mL). The ether layer was washed with water, brine and dried (Na_2SO_4). Concentration and purification afforded **9** (3.83 g, 86% yield) as a pale yellow solid, mp 89-90 °C; ^1H NMR: δ 1.78 (s, 3H), 3.45 (s, 1H), 3.53 (s, 3H), 3.60 (s, 3H), 3.64 (s, 3H), 3.68 (s, 3H); IR: 1780, 1745 cm^{-1}; FABMS: m/z 421 (M+1), 385 (base peak); HRMS: calcd. for $C_{14}H_{16}Cl_3O_6$ (M-Cl) 385.0013 found 385.0017

1,4,5,6-Tetrachloro-3-*endo*-hydroxymethyl-7,7-dimethoxy-3-methylbicyclo[2.2.1]hept-5-en-2-*endo*-ylmethanol (10):

To a solution of **9** (3.5 g, 8.3 mmol) in dry ether (40 mL) was added LAH (475 mg, 12.5 mmol) portionwise at 0 °C. The reaction mixture was refluxed for 20 h. After cooling, excess LAH was quenched with ethyl acetate and the mixture was treated successively with H_2O (0.5 mL), 15% aq NaOH solution (0.5 mL) and H_2O (1.5 mL). It was stirred for 2 h and filtered and washed properly with EtOAc. The combined filtrate and washings was concentrated under vacuum and the residue was purified by column chromatography to get **10** (2.52 g, 83% yield) as a white solid, mp 119-120 °C, ^1H NMR : δ 1.54 (s, 3H), 2.74 (dd, $J_1 = J_2 = 2.7$ Hz, 1H), 3.52 (s, 3H), 3.63 (s, 3H), 3.40-4.20 (m, 4H); IR: 3500 cm^{-1}; FABMS: m/z 365 (M+1), 329, 267, 149; HRMS: calcd. for $C_{12}H_{17}O_4Cl_4$ 364.9881, found 364.9881

10,10-Dimethoxy-2-methyl-4-oxatricyclo[5.2.1.$0^{2,6}$]dec-8-ene-2,6-*endo,endo*-3,5-dione (12):

In a 3 litre two necked round bottomed flask, fitted with a condenser, KOH guard tube and a septum, liquid NH_3 (2 litre) was collected and a solution of **7** (37.4 g, 0.1 mol) in THF (100 mL) and EtOH (30 mL) was added slowly. Small pieces of freshly cut sodium were introduced to the reaction mixture with stirring till blue color persisted for 30 min. Then the reaction mixture was quenched with solid NH_4Cl (5 g). Ammonia was allowed to escape and crushed ice was added to the residue. The solution was acidified (pH 1-2) with 50% aq HCl and was extracted several times with EtOAc. The organic layer was washed with brine and dried (Na_2SO_4) and concentrated to get **12** (15.2 g, 64% yield) as a solid. Small amount of **12** was crystallized from hexane/ chloroform (3:2) as colourless crystals, mp 128-129 °C; ^{1}H NMR: δ 1.66 (s, 3H), 2.96 (m, 1H), 3.15 (s, 3H), 3.19 (m, 1H), 3.25 (s, 3H), 3.44 (m, 1H), 6.22 (m, 1H), 6.38 (m, 1H); ^{13}C NMR: δ 19.26, 49.23, 50.06, 50.32, 52.01, 52.27, 121.04, 131.49, 136.41, 171.10, 174.67; IR: 2975, 1860, 1780, 1100, 920 cm^{-1}; EIMS: m/z 238 (M^+), 223, 210, 165, 91, 77; HRMS: calcd. for $C_{12}H_{14}O_5$ 238.0841, found 238.0836

3-*endo*-Hydroxymethyl-7,7-dimethoxy-3-methylbicyclo[2.2.1]hept-5-en-2-*endo*-ylmethanol (11):

Procedure-I: Following the same procedure as mentioned for compound **12**, compound **11** (1.16 g, 74% yield) was obtained from compound **10** (2.5 g, 6.9 mmol) as a viscous liquid.

Procedure-II: Compound **12** (23.8 g, 0.1 mol) was dissolved in THF (300 mL) in a two necked 1 litre round bottomed flask, fitted with a reflux condenser and a $CaCl_2$ guard tube. To this well stirred solution, LAH (5.7 g, 0.15 mol) was added portionwise for 2 h. After stirring for 12 h at room temperature, excess LAH was quenched with ethyl acetate and the mixture was treated successively with H_2O (5.7 mL), 15% aq NaOH solution (5.7 mL) and H_2O (17.1 mL). It was stirred for 2 h and filtered and washed properly with EtOAc. The combined filtrate and washings were concentrated under vacuum to get viscous liquid **11** (18.7 g, 82% yield); ^{1}H NMR: δ 1.45 (s, 3H), 2.34 (m, 1H), 2.43 (m, 1H), 2.76 (m, 1H), 3.08 (s, 3H), 3.21 (s, 3H), 3.10-3.68 (m, 4H), 6.02 (m, 1H), 6.15 (m, 1H); IR: 3460 cm^{-1}; Anal. calcd. for $C_{12}H_{20}O_4$: C 63.14, H 8.83; found : C 63.25, H 8.78

5,6-*endo,endo*-Di(benzyloxymethyl)-7,7-dimethoxy-5-methylbicyclo[2.2.1]hept-2-ene (13):

To a well stirred suspension of freshly activated NaH (4.2 g, 0.175 mol) in THF (200 ml) at 0 °C was added dropwise a solution of **11** (16.0 g, 0.07 mol) in THF (100 mL). After 1 h, tetrabutylammonium iodide (1 g) was introduced and then benzyl bromide (16.6 ml, 0.14 mol) was added dropwise. The reaction mixture was stirred overnight at room temperature and quenched with aq NH_4Cl solution and extracted with ether (3x200 mL). The combined organic layer was dried (Na_2SO_4), concentrated and column chromatographed to get **13** (24.9 g, 87% yield) as a pale yellow oil; ^{1}H NMR: δ 1.40 (s, 3H), 2.31 (m, 1H), 2.62 (m, 1H), 2.85 (m, 1H), 3.05 (s, 3H), 3.16 (s, 3H), 2.98-3.28 (m, 4H), 4.30 (s, 2H), 4.36 (AB_q, J= 11.1 Hz, 2H), 5.92 (m, 1H), 6.11 (m, 1H), 7.20 (m, 10H); Anal. calcd. for $C_{26}H_{32}O_4$: C 76.44, H 7.89; found : C 76.39, H 7.92

5,6-*endo,endo*-Di(benzyloxymethyl)-5-methylbicyclo[2.2.1]hept-2-en-7-one (14):

To a solution of **13** (20.4 g, 0.05 mol) in dry acetone (100 mL), PTSA (1 g) was added and the solution was stirred at room temperature for 6 h. Acetone was removed in rotavapor and the residue was diluted with ether (300 mL). The ether layer was washed with aq $NaHCO_3$ solution, water and brine and dried (Na_2SO_4). Concentration and chromatographic purification provided **14** (16.65 g, 92% yield) as a viscous liquid; ^{1}H NMR: δ 1.28 (s, 3H), 2.25 (m, 1H), 2.72 (m, 1H), 3.0-3.46 (m, 5H), 4.41 (AB_q, J= 13.6 Hz, 4H), 6.4 (m, 2H), 7.2-7.4 (m, 10H); IR: 1780 cm^{-1}; FABMS: m/z 363 (M+1), 91; Anal. calcd. for $C_{24}H_{26}O_3$: C 79.53, H 7.23; found : C 79.46, H 7.32.

(1R,4S,5R,6S)-5,6-Di(benzyloxymethyl)-4-hydroxy-5-methyl-2-cyclohexene-1-carboxylic acid (15):

To a solution of **14** (10.4 g, 28.7 mmol) in MeOH (200 mL), a solution of NaOH (3.45 g, 86.3 mmol) in water (20 mL) was added with stirring at 0 °C. Then 30% H_2O_2 (13 mL, 115 mmol) was added dropwise for 30 min. The reaction mixture was stirred for 48 h at room temperature. Excess H_2O_2 was quenched with aq solution of sodium metabisulphite. Methanol was distilled off and the aqueous layer was acidified with 3N HCl and extracted with ethylacetate (4x100 mL). The organic layer was washed with brine and dried (Na_2SO_4). Concentration and purification afforded **15** as major isomer (7.75 g, 68% yield) as a viscous liquid; ^{1}H NMR: δ 1.12 (s, 3H), 2.56 (m, 1H), 3.14-3.68 (m, 5H), 4.07 (br s, 1H), 4.28-4.56 (m, 4H), 6.0 (m, 2H), 7.25 (m, 10H); IR: 3540, 3480-2550 (br), 1710 cm^{-1}; FABMS : m/z 419 (M+23), 91; HRMS : calcd. for $C_{24}H_{28}O_5Na$ 419.1835, found 419.1822

(1R,4S,5R,6S)-Methyl 5,6-di(benzyloxymethyl)-4-hydroxy-5-methyl-2-cyclohexene-1-carboxylate (16):

To a solution of **15** (8 g, 20.2 mmol) in THF (50 mL) at 0 °C was added dropwise a yellow ethereal solution (100 mL) of diazomethane (obtained from NMU (8.32 g, 80.8 mmol) and 50 mL of 50% aq KOH solution at -5 °C). After stirring for 1 h at the same temperature, the solvents were removed and the residue was purified by column chromatography to get **16** (7.7 g, 93% yield) as a viscous liquid; ^{1}H NMR : δ 1.11 (s, 3H), 2.56 (m, 1H), 3.22 (m, 1H), 3.30-3.73 (m, 4H), 3.60 (s, 3H), 4.05 (br s, 1H), 4.42 (m, 4H), 5.80 (m, 2H), 7.28 (m, 10H); IR: 3450, 1735 cm^{-1}; CIMS: m/z 411 (M+1), 393, 285, 195, 91; HRMS : calcd. for $C_{25}H_{31}O_5$ 411.2172, found 411.2179

(1S,4R,5S,6R)-5,6-Di(benzyloxymethyl)-6-methyl-4-methyloxycarbonyl-2-cyclohexenyl acetate (17):

To a solution of **16** (410 mg, 1.0 mmol), Et_3N (0.28 mL, 2.0 mmol) and DMAP (25 mg) in DCM (10 mL) was added Ac_2O (0.14 mL, 1.5 mmol) dropwise at 0 °C. After stirring for 2 h, the reaction mixture was quenched with aq $NaHCO_3$ solution and diluted with DCM. The organic layer was separated and washed with water, brine and dried (Na_2SO_4). Solvent was removed and the residue was chromatographed to get **17** (411 mg, 91% yield) as a viscous liquid; ^{1}H NMR: δ 1.09 (s, 3H), 2.04 (s, 3H), 2.60 (m, 1H), 3.20 (m, 1H), 3.37-3.70 (m, 4H), 3.58 (s, 3H), 4.38 (m, 4H), 5.19 (d, J= 1.4 Hz, 1H), 5.83 (s, 2H), 7.25 (m, 10H); IR : 1740, 1735 cm^{-1}; FABMS : m/z 475 (M+23), 91; Anal. calcd. for $C_{27}H_{32}O_6$: C 71.66, H 7.13; found : C 71.48, H 7.22.

7,8-*endo,endo*-Di(benzyloxymethyl)-8-methyl-3-oxabicyclo[2.2.2]oct-3-en-2-one (18):

A mixture of hydroxy acid **15** (2.2 g, 5.56 mmol), Ac_2O (1.1 mL, 11.67 mmol), anhydrous NaOAc (1.14 g, 13.9 mmol) and dry benzene (30 mL) was heated under reflux with vigorous stirring. After 1 h, ice cold water was added to it and the organic phase was separated. The aq layer was extracted with additional ethyl acetate (2x25 mL). The combined organic layer was washed with aq $NaHCO_3$ solution, water and brine and dried (Na_2SO_4), Concentration and chromatographic separation over silica gel furnished lactone **18** (1.74 g, 83% yield) as a white solid. Small amount of **18** was crystallized from acetone as white needles, mp 79-80 °C; ^{1}H NMR: δ 1.38 (s, 3H), 2.06 (m, 1H), 3.06-3.46 (m, 4H), 3.55 (m, 1H), 4.40 (m, 4H), 4.96 (m, 1H), 6.23-6.46 (m, 2H), 7.20-7.40 (m, 10H); ^{13}C NMR: δ 23.91, 43.51, 43.91, 44.11, 68.23, 72.94, 73.30, 73.60, 80.59, 126.80-133.42 (12 lines), 137.72, 137.91, 173.82; IR: 1755 cm^{-1}; CIMS: m/z 379 (M+1), 227, 181, 91; HRMS: calcd for $C_{24}H_{27}O_4$ 379.1909, found 379.1914

(1R,4S,5R,6S)-5,6-Di(benzyloxymethyl)-4-hydroxy-5-methyl-2-cyclohexenylmethanol (19):

To a well stirred suspension of LAH (0.32 g, 8.5 mmol) in dry THF (15 mL) at 0 °C was added dropwise a solution of **16** (3.48 g, 8.5 mmol) in dry THF (15 mL). The reaction mixture was stirred overnight at room temperature and then worked up following the same procedure as described for compound **10**. The crude

product was purified by column chromatography to get **19** (2.66 g, 82% yield) as a highly viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.18 (s, 3H), 1.94 (m, 1H), 2.14 (m, 1H), 3.12-3.86 (m, 7H), 4.12-4.56 (m, 4H), 5.64 (m, 1H), 5.88 (m, 1H), 7.12-7.42 (m, 10H); IR : 1750 cm^{-1}; FABMS : m/z 405 (M+23), 383 (M+1), 91; HRMS : calcd. for $C_{24}H_{31}O_4$ 383.2222, found 383.2224

(1R,4S,5R,6S)-5,6-Di(benzyloxymethyl)-4-(3,5-dinitrophenylcarbonyloxy)-1-(3,5-dinitrophenylcarbonyloxymethyl)-5-methyl-2-cyclohexene (20):

To a solution of **19** (100 mg, 0.26 mmol) and DMAP (82 mg, 0.67 mmol) in DCM (10 mL) at 0 °C was added 3,5-dinitrobenzoyl chloride (138 mg, 0.60 mmol) portionwise. After stirring for 4 h, the reaction mixture was quenched with aq $NaHCO_3$ solution. DCM layer was separated, washed with water and brine and dried (Na_2SO_4). Concentration and chromatography afforded **20** (163 mg, 81% yield) as a pale yellow solid, mp 124-125 °C; ^{1}H NMR: δ 1.24 (s, 3H), 2.16 (m, 1H), 2.80 (m, 1H), 3.45-3.84 (m, 4H), 4.35-4.70 (m, 6H), 5.62 (d, J= 1.8 Hz, 1H), 6.03 (s, 2H), 7.10-7.38 (m, 10H), 8.90-9.20 (m, 6H); IR : 1730 cm^{-1}; FABMS: m/z 771 (M+1), 391, 91; HRMS : calcd. for $C_{38}H_{35}O_{14}N_4$ 771.2150, found 771.2143

(1R,4S,5R,6S)-Methyl 4-benzyloxy-5,6-di(benzyloxymethyl)-5-methyl-2-cyclohexene-1-carboxylate (22):

To a solution of **16** (7.2 g, 17.6 mmol) in DCM-cyclohexane (1:2, 60 mL) was added benzyl trichloroacetimidate (6.64 g, 26.3 mmol) and camphor sulfonic acid (408 mg, 1.76 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 20 h. The precipitated trichloroacetamide was filtered off. To the filtrate ice-water was added and extracted with DCM. DCM layer was washed with water and brine and dried (Na_2SO_4). Concentration followed by column chromatography afforded **22** (6.76 g, 77% yield) as a viscous liquid; ^{1}H NMR: δ 1.14 (s, 3H), 2.74 (m, 1H), 3.27 (m, 1H), 3.40-3.73 (m, 4H), 3.63 (s, 3H), 3.84 (m, 1H), 4.30-4.56 (m, 6H), 5.70-5.98 (m, 2H), 7.26 (m, 15H); IR: 1745 cm^{-1}; FABMS: m/z 523 (M+23), 501 (M+1), 393, 181, 91, 77; HRMS : calcd. for $C_{32}H_{36}O_5$ 500.2563; found 500.2533.

(1R,4S,5R,6S)-4-Benzyloxy-5,6-di(benzyloxymethyl)-5-methyl-2-cyclohexenylmethanol (23):

Alcohol **23** was obtained as a syrupy liquid in 82% yield from **22** (5.0 g, 10 mmol) using LAH (0.38 g, 10 mmol) in THF (60 mL) employing the same procedure as described for **11** (procedure-II). ^{1}H NMR: δ 1.26 (s, 3H), 2.10-2.36 (m, 2H), 3.16-3.85 (m, 7H), 4.35-4.70 (m, 6H), 5.72-6.02 (m, 2H), 7.15-7.42 (m, 15H); IR: 3450 cm^{-1}; FABMS: m/z 495 (M+23), 181, 91; HRMS: calcd for $C_{31}H_{36}O_4Na$ 495.2511, found 495.2524

(1R,2S,3R,4S,6R)-4-Benzyloxy-2,3-di(benzyloxymethyl)-6-hydroxy-3-methylcyclohexylmethanol (24):

A 100 mL two necked flask, fitted with a septum inlet, was charged with tetramethylethylene (688 mg, 8.2 mmol) in dry THF (5 mL) under nitrogen atmosphere. The flask was cooled to -10 °C using freezing mixture and 1M BH_3.THF complex (9.2 mL) was added slowly. After stirring for 1 h at 0 °C, the resulting solution containing thexylborane was syringed out under nitrogen and introduced dropwise to a solution of **23** (2.6 g, 5.5 mmol) in dry THF (10 mL) at 0 °C under nitrogen. The reaction mixture was stirred for 2 h at 0 °C and then 4 h at 25 °C. The excess borane was quenched by carefull addition of water and then treated with 20% aq NaOH solution (5 mL). To it 30% H_2O_2 (5 mL) was added slowly and stirred overnight at room temperature. Excess H_2O_2 was quenched with aq sodium meta-bisulphite solution and the aqueous layer was extracted with ethyl acetate (3x25 mL). The organic layer was washed with water, brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography to get **24** (1.92 g, 71% yield) as a viscous liquid; ^{1}H NMR : δ 1.10 (s, 3H), 1.40-1.60 (m, 2H), 1.88 (m, 1H), 2.05 (m, 1H), 3.25-3.50 (m, 4H), 3.52-3.81 (m, 3H), 4.05 (br s, 1H), 4.32-4.68 (m, 6H), 7.28 (m, 15H); IR : 3450 (br) cm^{-1}; FABMS m/z 491 (M+1), 383, 107, 91; HRMS : calcd. for $C_{31}H_{39}O_5$ 491.2798, found 491.2793.

(1R,2S,3R,4S,6R)-4-Benzyloxy-2,3-di(benzyloxymethyl)-6-hydroxy-3-methyl-1-(4-methylphenylsulfonyl-oxymethyl)cyclohexane (25):

To a solution of **24** (1.5 g, 3.1 mmol), pyridine (0.4 g, 5.1 mmol) and DMAP (50 mg) in DCM (20 mL) at 0 °C was added in portions tosyl chloride (0.67 g, 5.3 mmol). After stirring for 6 h at room temperature, the reaction mixture was quenched with aq $NaHCO_3$ solution. DCM layer was separated and washed successesively with saturated aq solution of $CuSO_4$, water, brine and dried over Na_2SO_4. The solvent was removed and the residue was column chromatographed over silica gel to get **25** (1.46 g, 74% yield) as a syrup; ^1H NMR: δ 1.10 (s, 3H), 1.44-1.82 (m, 2H), 2.12 (m, 1H), 2.28 (m, 1H), 2.42 (s, 3H), 3.32-3.54 (m, 4H), 3.60-3.78 (m, 2H), 3.86-4.12 (m, 2H), 4.28-4.66 (m, 6H), 7.27 (m, 17H), 7.75 (d, J= 8.0 Hz, 2H); IR : 3490 cm^{-1}; Anal. calcd. for $C_{38}H_{44}O_7S$: C 70.78, H 6.88, S 4.97; found : C 70.72, H 6.88, S 4.88

(1R,2R,3S,4R,5S)-5-Benzyloxy-3,4-di(benzyloxymethyl)-4-methyl-2-(4-methylphenylsulfonyl-oxymethyl)cyclohexyl acetate (26):

To a solution of **25** (0.5 g, 0.78 mmol), Et_3N (0.17 mL, 1.2 mmol) and DMAP (25 mg) in DCM (10 mL) was added Ac_2O (0.09 mL, 0.94 mmol) dropwise at 0 °C. After stirring for 2 h, the reaction mixture was quenched with aq $NaHCO_3$ solution and diluted with DCM. The organic layer was separated and washed with water, brine and dried (Na_2SO_4). Solvent was removed and the residue was chromatographed to get **26** (0.44 g; 83% yield) as a viscous liquid; ^1H NMR: δ 1.06 (s, 3H), 1.65-1.81 (m, 2H), 1.92 (s, 3H), 2.05 (m, 1H), 2.28 (m, 1H), 2.44 (s, 3H), 3.30-3.58 (m, 4H), 3.68-3.82 (m, 1H), 3.84-4.20 (m, 2H), 4.24-4.60 (m, 6H), 5.10 (m, 1H), 7.10-7.40 (m, 17H), 7.74 (d, J= 8.1 Hz, 2H); IR : 1740 cm^{-1}; FABMS : m/z 687 (M+1); HRMS : calcd. for $C_{40}H_{47}O_8S$ 687.2992, found 687.2988

(1R,2R,3S,4R,5S)-5-Benzyloxy-3,4-di(benzyloxymethyl)-4-methylperhydrobenzo[b]oxete (27):

To a stirred solution of **26** (200 mg, 0.31 mmol) in THF (5 mL) was added freshly active (by washing with dry petroleum ether) NaH (11 mg, 0.46 mmol) at 0 °C and allowed to stir at room temperature for 12 h. The reaction mixture was quenched with cold water and extracted with ether. The extract was washed with water, brine and dried over Na_2SO_4. Solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography to afford **27** (112 mg, 76% yield) as a highly viscous liquid; ^1H NMR: δ 1.07 (s, 3H), 1.85-1.89 (m, 1H), 1.98-2.01 (m, 1H), 2.27-2.31 (m, 1H), 2.42-2.56 (m, 1H), 3.36-3.58 (m, 4H), 3.73-3.79 (m, 1H), 4.09-4.18 (m, 2H), 4.37-4.55 (m, 6H), 4.61-4.66 (m, 1H), 7.22-7.40 (m, 15H); ^{13}C NMR : δ 22.65, 35.51, 36.71, 40.60, 48.22, 65.94, 68.29, 71.32, 72.81, 73.80, 73.93, 76.80, 83.76, 127.52-128.55 (7 lines), 137.62, 137.89, 138.43; FABMS: m/z 495 (M+23), 365, 107, 91, 77; HRMS : calcd. for $C_{31}H_{36}O_4Na$ 495.2511, found 495.2514.

Acknowledgement: One of us (PKS) is thankful to CSIR, New Delhi for financial assistance.

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