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Diastereoselective Triple Radical Cyclization of a Bromomethyldimethylsilyl Allyl Ether

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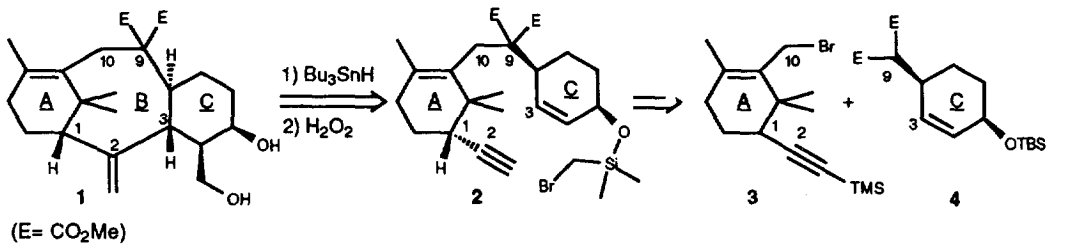
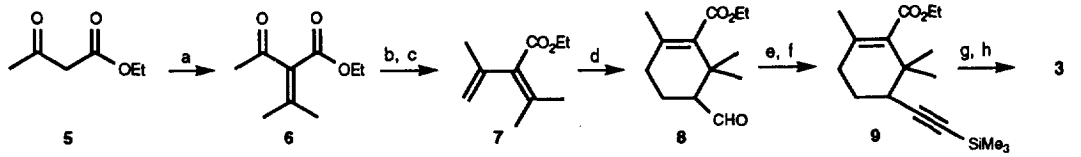
Abstract: *A convergent strategy to construct the B-ring in an AC → ABC cyclization to the taxane framework was tested. The bicyclic bromomethyldimethylsilyl ether 2 was efficiently synthesized by a sequence proceeding through the alkylation of the C-ring malonate 4 by the hindered A-ring bromide 3. The desired tandem 5-exo-trig/8-exo-dig cyclization of 2 to diol 1 was not observed. An alternative pathway was indicated by isolation of crystalline tetracyclic diastereomers 12a and 12b, derived by a diastereoselective sequence of three radical cyclizations.* Copyright © 1996 Elsevier Science Ltd

The structurally challenging and clinically important antitumor agent taxol has been the focus of intense synthetic interest over the past decade; three total syntheses have recently been reported.[1] In 1986 we described the first construction of the tricyclic taxane framework by a low-yield McMurry cyclization to form the C(9)-C(10) bond.[2] We now report a test of an alternative B-ring closure strategy employing a 5-*exo-trig*/8-*exo-dig*[3] tandem cyclization retrosynthetically outlined in Scheme 1. The tricyclic diol **1**, an advanced model toward taxol, would arise by *n*-Bu_3SnH-initiated tandem radical cyclization[4] of the bromomethylsilane **2** through a cyclosiloxane easily transformed to the 1,3-diol **1** by a Tamao oxidation.[5] The C(9)-C(10) bond in **2** would be formed by alkylation of the C-ring malonate **4** by the hindered A-ring allyl bromide **3**.



Scheme 1

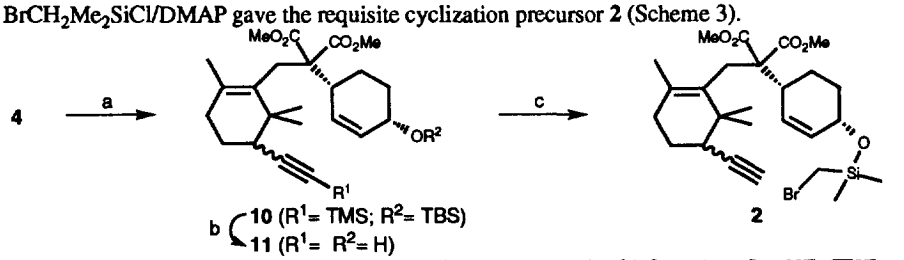
Malonate **4** was prepared by the totally regio- and stereoselective reaction of dimethyl malonate anion and the monoepoxide of 1,3-cyclohexadiene in the presence of 5 mol% of $Pd(PPh_3)_4$.[6] Allylic bromide **3** was synthesized as in Scheme 2, using a Lewis acid-catalyzed Diels-Alder reaction between diene **7** and acrolein.[7]



a) 1.5 equiv acetone; 1.35 equiv Ac_2O; 0.14 equiv $ZnCl_2$; 60 °C; 72 h; (42%); b) 1.1 equiv CH_3MgBr; Et_2O; 0 °C to rt; 1 h; c) 0.2 equiv p-TsOH; 60 °C; 1 h; (70%; 2 steps); d) 3.5 equiv acrolein; 3 equiv BF_3•Et_2O; CH_2Cl_2; -78 °C; 2 h; (81%); e) 4 equiv PPh_3; 2 equiv CBr_4; CH_2Cl_2; 0 °C; 5 min.; f) 2 equiv n-BuLi; THF; -78 °C; 1 h then 1 equiv TMSCl; -78 °C to rt; (98%; 2 steps); g) 2.2 equiv DiBAl-H; hexanes; 0 °C; 10 min.; (77%); h) 0.35 equiv PBr_3; pyridine cat.; Et_2O; -30 °C, 2 h to rt (over 3 h) then 40 °C; 30 min.; (91%).

Scheme 2

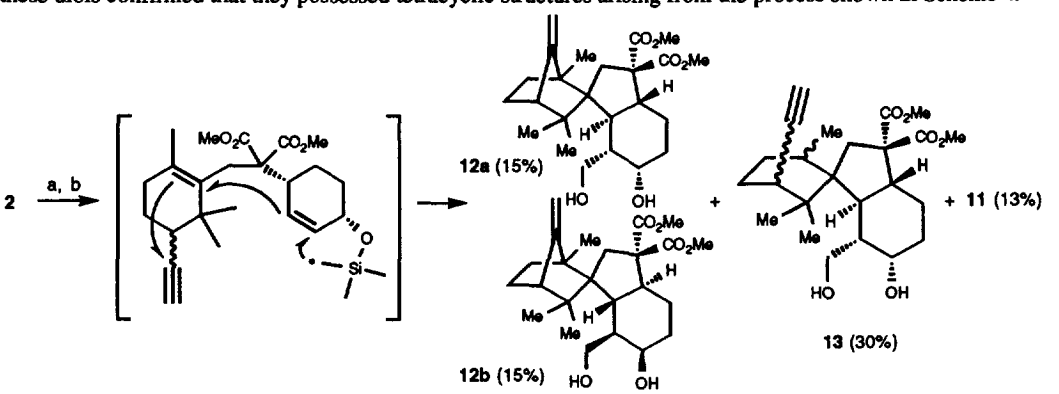
The sodium salt of **4** reacted smoothly with bromide **3** in refluxing THF to give **10** in 83% yield as a 1:1 mixture of inseparable diastereomers. Double desilylation of **10**, followed by the resilylation of the OH in **11** with $BrCH_2Me_2SiCl$/DMAP gave the requisite cyclization precursor **2** (Scheme 3).



a) 1 equiv NaH; THF; rt 1 h then 1equiv 3; rt to reflux; 16 h; (83%); b) 5 equiv n-Bu_4NF; THF; rt; 16 h; (89%); c) 1.1 equiv Et_3N; 0.1 equiv 4-DMAP; 1 equiv $(CH_3)_2CH_2BrSiCl$; CH_2Cl_2; 0 °C; 15 min.; (94%).

Scheme 3

Radical cyclization was performed by syringe pump addition of *n*-Bu3SnH to a boiling benzene solution of **2** in the presence of AIBN catalyst.[8] Careful chromatography of the reaction products after Tamao oxidation led to 13% of recovered alcohol **11** and two isomeric crystalline diols **12a** (mp 182-184°) and **12b** (mp 156-158°). Proton and ^{13}C-NMR analyses of these new products indicated that cyclizations had occurred, but that the tricyclic taxane framework had not been achieved.[9] Single crystal X-ray structure determinations on these diols confirmed that they possessed tetracyclic structures arising from the process shown in Scheme 4.



a) 1.3 equiv Bu_3SnH;0.1 equiv AIBN; PhH; 80 °C; 10 h; b) 20 equiv H_2O_2 (30%); 5 equiv $KHCO_3$; THF/MeOH (1/1); 60 °C; 30 min.

Scheme 4

Here the initial α-silyl radical undergoes three consecutive 5-*exo* cyclizations to give the separable diols **12a, 12b** in 1:1 ratio (arising from the uncontrolled propargylic center in the precursor **2**). The observed pathway involves addition of a cyclohexyl radical intermediate to a highly hindered, unactivated tetrasubstituted double bond, reportedly an unfavorable process.[10] This gives a spiro junction, and the resulting tertiary radical is trapped by the terminal alkyne. Indeed, one of the chromatographic fraction provided ca. 30% yield of the tricyclic structure **13** as a mixture of 4 inseparable diastereomers. These derive from reduction of the putative tertiary radical prior to its addition to the alkyne.

The conversion of bicyclic bromomethylsilane **2** to **12a** and **12b** represents the one-pot formation of three C-C bonds from the stereocontrolled generation of four stereogenic centers with three contiguous quaternary carbons. Although this approach did not yield the desired B-ring, the successful alkylation of malonate **4** by **3** offers a valuable entry to C(9)-C(10) linked AC bicyclic precursors. We are exploring alternative tactics to form the elusive C(2)-C(3) bond in related systems.

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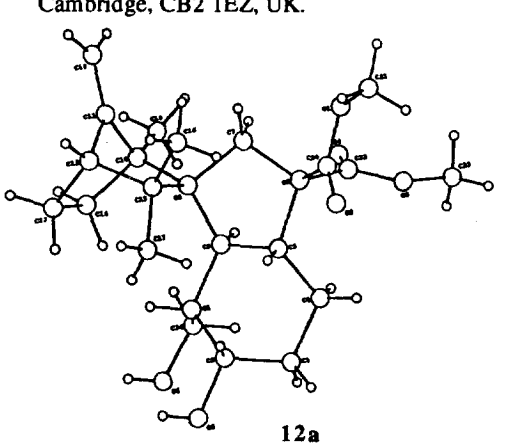
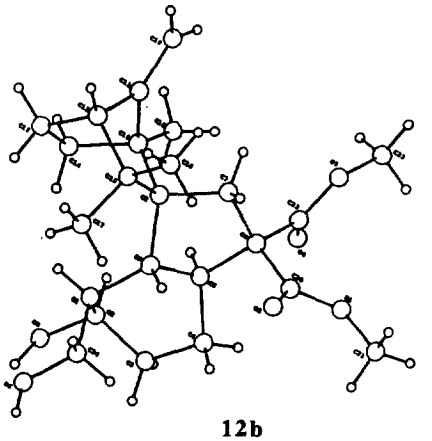
(8) In a typical procedure, a benzene solution (5 mL) of *n*-Bu_3SnH (350 μL, 1.3 mmol) containing AIBN (14 mg, 0.1 mmol) was added by a syringe pump over 5.5 h ($2x10^{-4}$ mol/h) to a solution of **2** (540 mg, 1.0 mmol; 1/1 mixture of diastereomers) in refluxing benzene (50 mL) under nitrogen. After completion of the addition, the mixture was allowed to reflux for 5 additional hours. The solution was evaporated in vacuo and the crude mixture was dissolved in 15 mL of a 1/1 mixture of THF/MeOH with $KHCO_3$ (500 mg, 5 mmol) and was allowed to warm to 60 °C. Hydrogen peroxide (30% wt/H_2O; 2.1 mL, 20 mmol) was added dropwise and the resulting solution stirred at 60 °C for 30 min. Reaction mixture was cooled to 0 °C and quenched with 20 mL of a 10% $NaHSO_3$ solution. The mixture was filtered through Celite and extracted with diethyl ether (3x50 mL). Combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a colorless oil which was flash chromatographed (silica) with an 80/20 mixture of diethyl ether and hexanes as eluent to yield 63 mg of **12a** (15%) and 63 mg of **12b** (15%) as white solids. **12a**: R_f= 0.20 (80/20 Et_2O/Hex); mp 182-184 °C; ^{1}H-NMR (300 MHz, C_6D_6) δ 4.53 (s, 1 H), 4.49 (s, 1 H), 4.17-4.22 (m, 1 H), 3.73 (t, *J* = 10.5 Hz, 1 H), 3.58-3.62 (m, 1 H), 3.32 (s, 3 H), 3.18 (s, 3 H), 2.83 (d, *J* = 15.5 Hz, 1 H), 2.74-2.79 (m, 1 H), 2.72 (td, *J* = 13.6 and 4.3 Hz, 1 H), 2.28 (d, *J* = 15.5 Hz, 1 H), 2.17-2.24 (m, 1 H), 2.02-2.11 (m, 1 H), 1.55-1.85 (m, 4 H), 1.32-1.40 (m, 2 H), 1.18 (s, 3 H), 1.16 (s, 3 H), 0.90-1.10 (m, 2 H), 0.87 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 173.3, 172.8, 160.6, 95.4, 69.9, 66.3, 58.8, 56.5, 55.3, 52.4, 52.2, 50.9, 46.4, 42.7, 42.4, 42.3, 41.3, 31.8, 31.3, 25.8, 23.8, 22.8, 22.5, 15.0; IR (film) 3350, 3080, 3020, 2980,

1725, 1440, 1385, 1350, 1270, 1120, 1000, 895 cm^{-1}; MS (HRFAB), *m/e* calcd for $C_{24}H_{37}O_6$ (MH^+) 421.2590, measured, 421.2600. **12b**: R_f= 0.15 (80/20 Et_2O/Hex); m.p 156-158 °C; ^{1}H-NMR (300 MHz, C_6D_6) δ 4.55 (s, 1 H), 4.47 (s, 1 H), 4.25-4.29 (m, 1 H), 3.65-3.74 (m, 2 H), 3.33 (s, 3 H), 3.19 (s, 3 H), 3.05 (d, *J* = 15.5 Hz, 1 H), 2.71 (td, *J* = 13.9 and 4.0 Hz, 1 H), 2.62-2.70 (m, 1 H), 2.31-2.45 (m, 1 H), 2.10-2.15 (m, 1 H), 2.06 (d, *J* = 15.5 Hz, 1 H), 1.59-1.85 (m, 4 H), 1.16-1.41 (m, 4 H), 1.09 (s, 3 H), 1.07 (s, 3 H), 1.06 (s, 3 H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 172.7, 172.6, 161.9, 96.6, 69.9, 66.4, 57.7, 55.6, 54.4, 52.4, 52.1, 51.7, 47.4, 43.5, 43.1, 42.3, 41.7, 31.7, 30.6, 27.5, 23.9, 23.2, 22.2, 18.4; IR (film) 3350, 3080, 3020, 2980, 1725, 1440, 1385, 1350, 1270, 1120, 1000, 895 cm^{-1}; MS (HRFAB), *m/e* calcd for $C_{24}H_{37}O_6$ (MH^+) 421.2590 , measured, 421.2603.

(9) Relative stereochemistry in **12a** and **12b** was unambiguously established by X-ray crystallography of each diol after having been recrystallized from nitromethane. Atomic coordinates for **12a** and **12b** can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.



12a



12b

(10) It is known that steric influences do not depend on the steric hindrance of the alkyl centered radical but depend strongly on the position of the shielding group of the alkene. For example, it has been reported that the rate of the addition of a cyclohexyl radical on an α-t-butyl-substituted acrylate was reduced by a factor of approximatively 3000 vs. the unsubstituted acrylate: Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 967-967.

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