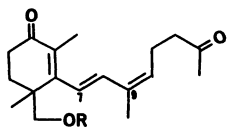
Stereospecific Synthesis of the Fungal Prohormone (±)-Trisporol B via the Palladium-Catalyzed Cross-Coupling Reaction of 1-Alkenylborane with 1-Haloalkene

Norio MIYAURA, Yoshitaka SATOH, Shoji HARA, and Akira SUZUKI*
Department of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo 060
(Received January 20, 1986)

Synopsis. The synthesis of the titled C_{18} apocarotenoid prohormone by means of palladium-catalyzed cross-coupling reaction between (*E*)-1-alkenylbis(1,2-dimethylpropyl)-borane (**10**) and (*Z*)-6-iodo-5-hepten-2-one ethylene acetal (**9**) is described. The reaction is highly stereoselective and the demanded (7*E*) and (9*Z*) double bonds are readily introduced.

The development of a simple and convenient method for the preparation of functionalized conjugated alkadienes and trienes has long been attracting much attention, since they would be promising versatile intermediates for the synthesis of naturally occurring biologically active compounds. Recently, we have reported that 1-alkenylboranes react with 1-alkenyl halides in the presence of palladium catalyst and base to give stereodefined conjugated alkadienes while preserving their *E* and *Z*-configurations.[1]

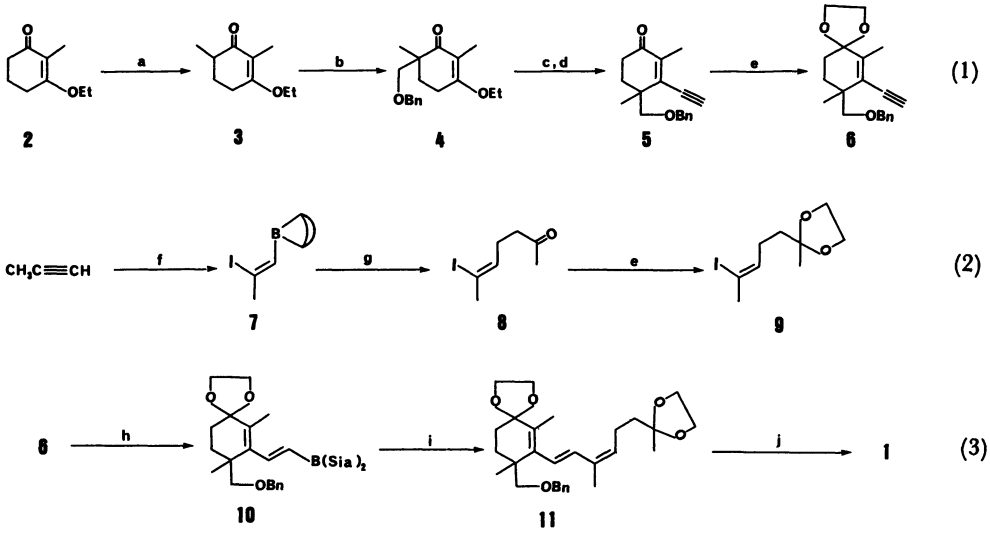
In this paper, we describe a stereospecific synthesis of the benzyl ether of a fungal prohormone (±)-trisporol B[2] (**1**, R=CH_2Ph) which involves the cross-coupling reaction between (*E*)-1-alkadienylborane (**10**) and (*Z*)-1-alkenyl iodide (**9**).



1 R = H, (±)-Trisporol B

The dienylborane derivative (**10**), required for the cross-coupling, was prepared via five steps from 2-methyl-3-ethoxy-2-cyclohexenone (**2**).[8] Thus, the methylation of **2** with lithium diisopropylamide (LDA) and methyl iodide in THF and HMPA, according to the method developed by Stork,[3] gave **3** in 91% yield as a white solid. Essentially the same procedure was applied for the benzyloxymethylation of **3** with LDA and benzyl chloromethyl ether to give **4** in 88% isolated yield. This enone **4** was then transformed into the enynone **5** by treatment with lithium trimethylsilylacetylide and the subsequent hydrolysis with aqueous hydrogen chloride. Desilylation[4] was performed with a saturated KF solution in 95% ethenol at room temperature in a quantitative yield. Subsequently, the carbonyl function of **5** was protected as its ethylene acetal. Thus, the overall yield from **2** to **6** was 56%, as shown in Eq. 1.

On the other hand, we have previously reported that the haloboration of terminal alkynes with 9-iodo-9-borabicyclo[3,3,1]nonane (B-I-9-BBN) proceeds highly regio- and stereoselectively to give the *syn*-adducts 9-[(*Z*)-2-iodo-1-alkenyl]-9-BBN's such as **7** in essentially quantitative yields, and the β-haloalkenyl-9-BBN (**7**) thus obtained reacts with α,β-unsaturated ketones via a Michael-type addition to yield haloalkenyl ketones like **8** in excellent yields.[5] This reaction sequence was applied to the synthesis of another necessary segment **9** for the cross-coupling (Eq. 2).



The coupling of these two fragments to **1** was carried out as outlined in Eq. 3. Namely, the enyne **6** in THF was subjected to hydroboration with bis(1,2-dimethylpropyl)borane[6] at room temperature by the usual procedure to give the dienylborane **10**. A mixture of **10** and the iodoalkene **9** in benzene containing $Pd(PPh_3)_4$[7] and sodium ethoxide was heated under reflux for 6 h in an atmosphere of nitrogen. The usual work-up and purification by TLC(silica gel–hexane) gave pure **11** in 52% yield, based on **6**. Finally, the deprotection of the ethylene acetal group with hydrogen chloride afforded the expected benzyl ether of trisporol B (**1**, R=CH_2Ph) as a pure form.

The present result clearly demonstrates that the novel two methodologies, the palladium-catalyzed cross-coupling reaction[1] and the haloboration-conjugate addition reaction,[5] both of which have been recently discovered by our group, provide a short step synthesis of trisporol B.

Experimental

The IR spectra were recorded on a Hitachi-Perkin Elmer Model 125 spectrometer. The ^1H NMR spectra of all compounds were measured with a Hitachi R-90H spectrometer (90 MHz) (solvent, $CDCl_3$; TMS as an internal reference). The measurement of mass spectra was carried out on a JEOL JMS-D 300 spectrometer (70 eV). Benzyl chloromethyl ether and trimethylsilylacetylene were commercial products and purified by distillation. THF was purified by distillation from benzophenone and sodium before use.

3-Ethoxy-2,6-dimethyl-2-cyclohexenone (3). To a solution of lithium diisopropylamide (LDA) (44 mmol) in THF (40 ml) was slowly added a solution of 3-ethoxy-2-methyl-2-cyclohexenone[8] (6.16 g, 40 mmol) in THF (20 ml) at −78 °C and the mixture was stirred for 1 h. To this solution was added HMPA (6 ml), and then methyl iodide (42 mmol) in THF (10 ml). The reaction mixture was stirred for 2 h at −78 °C, gradually warmed up to room temperature over 1 h, and then allowed to stand over night. The mixture was poured into ice water, extracted with ether, washed with brine, and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was chromatographed over silica gel with benzene/ethyl acetate (=10/1) to give **3** (6.1 g, 91%); Mp 49 °C; IR (nujol) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.14 (d, 3H, J=6.6 Hz), 1.34 (t, 3H, J=7.0 Hz), 1.70 (broad s, 3H), 1.8—2.4 (m, 3H), 2.4—2.7 (m, 2H), and 4.05 (q, 2H, J=7.0 Hz). Found: m/z 168.11495. Calcd for $C_{10}H_{16}O_2$: M, 168.11501.

6-Benzyloxymethyl-2,6-dimethyl-3-ethoxy-2-cyclohexenone (4). To a solution of LDA (36 mmol) in THF (30 ml) was slowly added a solution of the enone **3** (33 mmol) in THF (20 ml) at −78 °C and stirred for 1 h. Then, HMPA (5.5 ml) and benzyl chloromethyl ether (38 mmol) in THF (10 ml) were gradually added. The reaction mixture was stirred for 2 h at −78 °C, and then warmed up to room temperature. After the solution was allowed to stand overnight, a saturated brine solution was added. The mixture was extracted with benzene, washed with brine, and dried over $MgSO_4$. The chromatography over silica gel with benzene/ethyl acetate (=15/1) gave **4** (8.3 g, 88%); n_D^{20}=1.5410; IR (film), 1625, 1460, 1385, 1360, 1240, 1115, 740, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.08 (s, 3H), 1.33 (t, 3H, J=7.0 Hz), 1.69 (broad s, 3H), 1.7—2.2 (m, 2H), 2.4—2.6 (m, 2H), 3.32 (d, 1H, J=9.0 Hz), 3.66 (d, 1H, J=9.0 Hz), 4.03 (q, 2H, J=7.0 Hz), 4.49 (s, 2H), and 7.92 (s, 5H); Found: m/z 288.17359. Calcd for $C_{18}H_{24}O_3$: M, 288.17349.

4-Benzyloxymethyl-2,4-dimethyl-3-ethynyl-2-cyclohexenone (5) and Its Acetal (6). To a solution of trimethylsilylacetylene (20 mmol) in THF (20 ml) was added a solution of butyllithium in hexane (12.5 ml, 20 mmol) at −78 °C and the solution was stirred for 30 min. Anhydrous lithium bromide (6 mmol)[9] was added all at once, and then a solution of the enone **4** (14.3 mmol) in THF (10 ml). The reaction mixture was stirred for 1 h at −78 °C, and then warmed up to 0 °C over 1 h. After the solution was stirred for 1 h at 0 °C, aqueous 2 mol dm^{-3}-HCl (20 ml) was added slowly with vigorous stirring. After 20 min, the aqueous layer was separated and extracted with ether. The combined extracts were washed with a saturated brine solution, an aqueous 5% Na_2CO_3 solution and finally again with brine. After evaporation of the solvent, the residue was dissolved in 95% ethanol (100 ml) and treated with KF (9 g) for 3 h at room temperature. The removal of ethanol in vacuo (12 mmHg) gave a mixture of the product and an excess of KF. This mixture was extracted with benzene, washed with brine, dried over $MgSO_4$, and finally chromatographed over silica gel with benzene/ethyl acetate (=20/1) gave **5** (2.7 g, 70%), mp 57 °C; IR (nujol) 3260, 2150, 2090, 1670, 1590, 1100, 1025, 843, 730, and 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.22 (s, 3H), 1.99 (s, 3H), 1.6—2.6 (m, 4H) 3.36 (d, 1H, J=9.0 Hz), 3.64 (d, 1H, J=9.0 Hz), 4.53 (s, 2H), and 7.3 (s, 5H). Found: m/z 268.14526. Calcd for $C_{18}H_{20}O_2$: M, 268.14536.

A mixture of **5** (1.3 g, 4.8 mmol), ethylene glycol (6.3 mmol), trimethyl orthorformate (7 mmol), and a catalytic amount of p-toluenesulfonic acid in ether (20 ml) was stirred for 48 h at room temperature. After the usual work-up, the acetal was isolated by chromatography over silica gel with benzene/ethyl acetate (=20/1), 1.42 g (94%) of **6**; bp 160—165 °C/0.05 mmHg (the oven temperature of Kugelrohr) (1 mmHg=133.322 Pa); IR (neat) 3290, 2145, and 2095 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.14 (s, 3H), 1.9 (s, 3H), 1.5—2.1 (m, 4H), 3.13 (s, 1H), 3.34 (d, 1H, J=9.0 Hz), 3.48 (d, 1H, J=9.0 Hz), 3.99 (s, 4H), 4.52 (s, 2H), and 7.30 (s, 5H); Found: m/z 312.17185. Calcd for $C_{20}H_{24}O_3$: M, 312.17191.

(Z)-6-Iodo-5-hepten-2-one (8) and Its Acetal (9). The preparation of **8** from propyne was reported elsewhere,[5] which was protected as its ethylene acetal (**9**) by the usual procedure[10] by using ethylene glycol, methyl orthoformate, and p-TsOH in ether at room temperature. **9**: n_D^{18}=1.4980; IR (neat) 1670, 1150, 1055, 950, and 865 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.33 (s, 3H), 1.53—1.87 (m, 2H), 2.0—2.3 (m, 2H), 2.47 (s, 3H), 3.93 (s, 4H), and 5.43 (t, 1H, J=6.5 Hz).

The Benzyl Ether of (±)-Trisporol B (1, R=CH_2Ph). To a solution of **6** (1.8 mmol) in THF (2 ml) was added a solution of bis(1,2-dimethylpropyl)borane[6] in THF (4 ml of a 0.5 mol dm^{-3} solution, 2 mmol), and the mixture was stirred for 16 h at room temperature. After evaporation of the solvent in vacuo, the residue was dissolved in benzene (6 ml). To the solution of dienylborane **10** in benene thus obtained were added $Pd(PPh_3)_4$[7] (0.054 mmol), the alkenyl iodide acetal **9** (1.8 mmol) and a solution of sodium ethoxide in ethanol (1.8 ml of a 2 mol dm^{-3} solution), and then the mixture was refluxed for 6 h under N_2. After the flask was cooled to room temperature, NaOH (3 mol dm^{-3}, 2 ml) and 30%-H_2O_2 (0.5 ml) were added to decompose the unreacted borane. The product was then extracted with benzene, washed with a saturated brine solution, and dried ove $MgSO_4$. After evaporation of the solvent, the residue was chromatographed over silica gel with benzene/ethyl acetate (=10/1.5) to give **11** (0.435 g, 52%); n_D^{20}=1.4230; IR (film) 1663, 1075, 730, and 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.03 (s, 3H), 1.31 (s, 3H), 1.71 (s, 3H), 1.78 (broad s, 3H), 1.4—2.0 (m, 6H), 2.0—2.3 (m, 2H), 3.14 (d, 1H, J=9.0 Hz), 3.36 (d, 1H, J=9.0 Hz), 3.91 (s, 4H), 4.01 (s, 4H), 5.35 (t, 1H, J=7.0 Hz), 5.95 (d, 1H, J=16.3 Hz), 6.46 (d, 1H, J=16.3 Hz), and 7.29 (s, 5H); Found: m/z 468.28742.

Calcd for $C_{29}H_{40}O_5$: M, 468.28743.

A solution of **11** (0.101 g, 0.214 mmol) in THF (3 ml) was treated with aqueous 2 mol dm^{-3}-HCl (1 ml) for 6 h at room temperature. The product was extracted with ether, washed with brine, aqueous 5%-$NaHCO_3$, and finally with brine. TLC (silica gel) with benzene/ethyl acetate (=5/1) gave 75 mg (92%) of the benzyl ether of trisporol B (**1**, R=CH_2Ph): n_D^{20} =1.5650; λ_{max}^{EtOH}=301 nm; IR (neat) 1715, 1665, 1590, 1100, 965, 730, and 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.13 (s, 3H), 1.81 (broad s, 3H), 1.85 (s, 3H), 2.11 (s, 3H), 2.2—2.7 (m, 6H), 3.23 (d, 1H, J=9.0 Hz), 3.51 (d, 1H, J=9.0 Hz), 4.50 (s, 2H), 5.43 (broad t, 1H, J=7.2 Hz), 6.13 (d, 1H, J=16.0 Hz), and 6.60 (d, 1H, J=16.0 Hz); Found: m/z 380.23385. Calcd for $C_{25}H_{32}O_3$: M, 380.23397.

Although we could not compare the authentic sample of benzylether of trisporol B with the product **1** (R=CH_2Ph) obtained in this work, the spectral data of our benzyl ether are quite similar to those of trisporol B previously reported,[2b] except some points due to the benzyl ether group. For instance, the characteristic bands at 1715 and 1665 cm^{-1} in IR and λ_{max}^{EtOH}=301 nm in UV owing to the conjugated enone structure are almost super-imposable with those of trisporol B (1710 and 1665 cm^{-1}, and λ_{max}^{EtOH}=298 nm).[2b] The benzyl ether has the following ^1H NMR characteristics. The chemical shifts of vinylic protons in δ (7-H=6.60, 8-H=6.13, and 10-H=5.43) and the coupling constant (J_{7-8}=16 Hz) agree almost completely with those of trisporol B: Vinylic protons; 6.63, 6.20, and 5.40. J_{7-8}=16 Hz. Moreover, the chemical shifts of four methyl groups in the former compound, δ=1.13, 1.81, 1.85, and 2.11, are in fair agreement with those of trisporol B; 1.11, 1.81, 1.89, and 2.08.

From these spectral data, the structure of our product was concluded to be the benzyl ether of the expected compound.

References

1) N. Miyaura, K. Yamada, H. Suginome, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 972 (1985).

2) a) J. D. Bu'Lock, D. Drake, and D. J. Winstanley, *Phytochemistry*, **11**, 2011 (1972); b) M. P. Prisbylla, K. Takabe, and J. D. White, *J. Am. Chem. Soc.*, **101**, 762 (1979), and for the synthesis of related compounds, trisporic acid and its ester; c) B. M. Trost and P. L. Ornstein, *Tetrahedron Lett.*, **24**, 2833 (1983) and references cited therein.

3) G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).

4) P. J. Stang and M. Ladika, *Synthesis*, **1981**, 29.

5) Y. Satoh, H. Serizawa, S. Hara, and A. Suzuki, *J. Am. Chem. Soc.*, **107**, 5225 (1985).

6) H. C. Brown, "Organic Synthesis via Boranes," John Wiley & Sons, New York (1975), p. 29.

7) D. R. Coulson, *Inorg. Synth.*, **13**, 121 (1972).

8) R. D. Clark, J. E. Ellis, and C. H. Heathcock, *Synth. Commun.*, **3**, 374 (1973); A. B. Mekler, S. Ramachandran, S. Swaminathan, and M. S. Newman, *Org. Synth.*, **41**, 56 (1961); W. F. Gannon and H. D. Houe, *ibid.*, **40**, 41 (1960).

9) In the absence of lithium bromide, the yield of **5** was considerably low: L. Brandsma and H. D. Verkruijsse, "Synthesis of Acetylenes, Allenes and Cumulenes," Elsevier Scientific Pub. Co., New York (1981).

10) T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, New York (1981).