Tetrahedron Vol. 37, No. 14, pp. 2441 to 2444, 1981
Printed in Great Britain.

0040-4020/81/142441-04$02.00/0
Pergamon Press Ltd.

CARBOCYCLIC SYNTHESIS VIA BORANES: STEREOCHEMICAL IMPLICATIONS OF BORON ANNULATION

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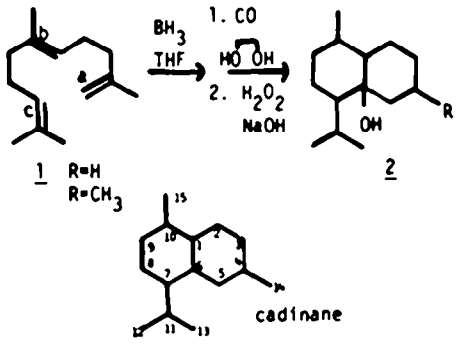
(*Received* 9 *March* 1981)

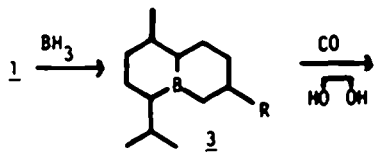
ABSTRACT - Boron annulation, hydroboration-carbonylation, of substituted 1,5,9-decatrienes was utilized to prepare the cadinane sesquiterpene system. Stereochemical aspects of the triene hydroboration process and the carbonylation reaction have been analyzed through glc separation of boronate esters. Structural assignments for these esters and their oxidation (H_2O_2/NaOH) products were made through high field ^{1}H-NMR and other physical and spectral considerations.

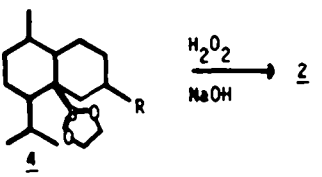
On initiating studies of boron annulations related to natural product synthesis we chose an initial model triene system which would provide technical skills as well as some predictive stereochemical information concerning the hydroboration-carbonylation process. Specifically, triene 1 was chosen as this model because of accessibility and the resemblance of the boron annulation products to natural cadinanes.



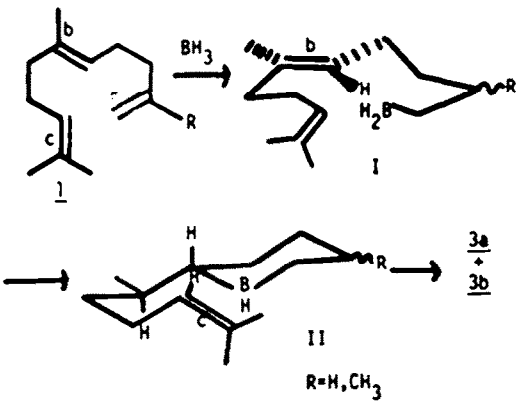
Triene 1 was prepared by coupling geranyl chloride with allylic Grignard reagents (methyallylmagnesium or allylmagnesium chloride) according to the procedure of Stork.[1] Hydroboration and carbonylation of triene 1 was effected under a variety of conditions yielding carbinol 2 as a mixture of isomers. For example, triene 1 (25 mmoles) was treated with $Et_3N{\cdot}BH_3$ (25 mmoles) in diglyme (5 mls) until ^{1}H-NMR of the reaction mixture was absent of vinyl proton resonances, forming 3 (60%, bp_{15}, 142°). Carbonylation of 3 with CO (1500 psi, 150°C) in ethylene glycol formed boronate 4 and then alcohol 2 after oxidation ($NaOH/H_2O_2$, 60% from 4, $bp_{0.3}$, 125°).[2]

The cadinol-like ring system was readily confirmed by selenium aromatization to known naphthalene systems.[5,6] Additional structural information was difficult to obtain on these unfunctionalized reaction products,

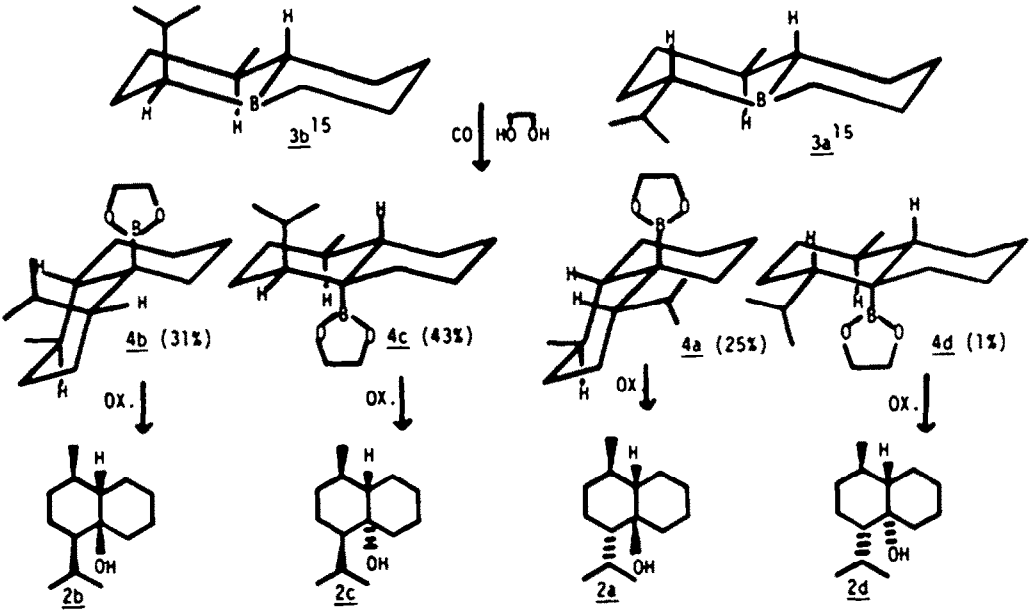




however, according to Brown,[3] one would anticipate a stepwise hydroboration following the well documented anti-Markownikoff, cis-addition format. Thus, the hydroboration of 5-(E)-6,10-dimethyl-1,5,9-undatriene (1, R=H)[11] is presumably initiated by a cis-addition to double bond "a", boron adding to the less hindered end of double bond "a" to give the monoalkylborane I. Intramolecular addition to trans double bond "b" in a cis-regioselective process must result in an eventual "trans" relationship for the C-1 and C-10 protons (cadinane numbering) in all bicyclic products (e.g., 4a, below). The final addition to double bond "c", forming 3, would be region but not stereoselective, with Drieding models suggesting 3b should be favored over 3a due to a restricted approach to double bond "c".[12] Finally, carbonylation of 3a and 3b would form the respective cis and trans decalin boronates (4a,b,c,d) and then alcohols (2a,b,c,d) upon oxidation.



methyl resonances (^{1}H-NMR δ = 0.66 and 0.67, J = 6.7 Hz). Models of 4b suggest boron and a methyl group are in close proximity in all chair conformers, suggestive of hindrance to oxidation; (4) Compounds 4a, 4c and 4d have methyl resonances which are very similar and models of these compounds suggest little shielding or deshielding effect by the boron ester group; (5) After oxidation of the purified boronate esters to alcohols, incremental addition of a lanthanide shift reagent ($Eu(fod)_3$) deshielded the following kinds of resonances (200MHz) relative to the majority of the hydrocarbon envelope: 2a two



Attempts to confirm these postulates by separations of carbinols 2 failed.[13] Success was finally realized via preparative gas chromatography (5% SE-30) of the boronate esters, 4, which resulted in four isomeric products whose preliminary structural assignments were based on the following: (1) The more rigid, planar trans decalin systems should elute later than cis decalins on a Silicone polymer column.[4] Isomers 4a and 4b should have comparable retention times and are expected to elute before trans isomers 4c and 4d; (2) Hydroboration should favor isomer 3b (vide supra) and therefore should yield more of cis and trans decalins 4b and 4c than 4a and 4d (74/26); (3) The most hindered boronate should be the most resistant to oxidation. Structure 4b was resistant to oxidation and also exhibited unusually shielded methynes and a methyl group, 2b one methyne and resolution of the isopropyl group into two doublets, 2c two methynes, and 2d one methyne.

In Brown's synthesis of 9-decalols from 1,4,8-nonatriene[9] 80% of the carbonylation products were cis decalins. If the structural assignments stated above are correct, one observes a similar high ratio of cis to trans decalins formed from intermediate 3a. In contrast, 3b presumably gives a much higher proportion of trans decalin due to steric influence of the C-7 isopropyl group which hinders approach of CO to the β-face of 3b. This suggests that oxygen ends up on the side of the boracycle which CO is likely to approach. Additional studies designed to confirm or refine this observation are now under way.

EXPERIMENTAL

IR data was recorded on either a Beckman Acculab I or a Beckman 4210 Spectrophotometer. ^{1}H-NMR were recorded on a Varian EM-360A Spectrometer using a tetramethylsilane internal standard. High field ^{1}H-NMR were recorded on a Bruker WP-200 (200 MHz) and a Bruker WH-400 (400 MHz) using a $CDCl_3$ internal standard. All coupling constants are in Hertz. ^{13}C-NMR were recorded on a Varian CFT-20 Spectrometer. Mass spectral data were obtained using a Hitachi-Perkin Elmer RMU-6. UV data was recorded on a Beckman Model 35 Spectrophotometer. All temperatures were uncorrected.

Cadalene - prepared according to the procedure of Takahashi,[5] the TLC,[5] ^{1}H-NMR,[6] IR and UV[7] and the melting point of its picrate [6] were in agreement with literature values. MS (70 eV) m/e 198 (57 re.%), 183 (100).

4-Isopropyl-1-methylanphthalene - formed by the same procedure as cadalene. Kugelrohr distillation (85°, 0.10 mm). TLC (silica gel, hexane) R_f = 0.57. IR (film) 2980, 2940, 2880, 1620, 1595, 1450, 1370, 805 cm^{-1}. ^{1}H-NMR (CCl_4) δ 1.3 (d, 6H, J = 7), 2.6 (S, 3H), 3.6 (m, 1H), 7.2 (m, 4H), 7.7 (m, 2H). MS (70 eV) m/e 184 (56 rel. %), 169 (100). $UV_{\lambda max}^{CH_3CN}$ 291, 230 nm.

5-(E)-6,10-Dimethyl-1,5,9-undacatriene (1)- prepared according to the method of Stork,[1] its IR, ^{1}H-NMR, and MS were in agreement with the published values. TLC (silica gel, hexane) R_f = 0.63. ^{13}C-NMR ($CDCl_3$) δ 138.6, 135.2, 130.9, 124.6, 124.0, 114.5, 39.9, 34.2, 27.6, 26.9, 25.7, 17.6, 16.0.

5-(E)-2,6,10-Trimethyl-1,5,9-undecatriene (1, R=CH_3) - prepared by the same method as (1, R=H), its IR, ^{1}H-NMR, and MS were in agreement with literature values.[8] TLC (silica gel, hexane) R_f = 0.63. ^{13}C-NMR ($CDCl_3$) δ 145.3, 134.9, 130.8, 124.6, 124.3, 110.1, 39.9, 38.0, 26.9, 26.4, 25.7, 22.4.

4-Desmethyl-6-cadinyl-1,3,2-dioxaborole (4, R=H) to a stirred solution of THF (30 mls) and $H_3BS(CH_3)_2$ (10 M, 1.68 mls, 16.8 mmol) at -40° under N_2 atmosphere was added 5-(E)-6,10-dimethyl-1,5,9-undecatriene (13.0 g, 16.8 mmol) in dry THF (10 mls) over 20 min. Stirring was continued for 1 hr. at -30°, 1 hr. at 0°, and overnight at room temperature.

The mixture was transferred by syringe to an autoclave under N_2 atmosphere and ethylene glycol (3.0 g, 48.2 mmol, 2.9 eq., 2.7 mls) was added. The autoclave was pressurized with CO (1600 psi) and heated for 1 hr. at 50°, then for 24 hrs. at 150°. After cooling to room temperature the mixture was added to hexane (150 mls), partitioned with H_2O (2 x 20 mls) and the organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Medium pressure liquid chromatography (silica gel, CH_2Cl_2) and subsequent Kugelrohr distillation (140°, 3 mm) afforded 0.95 g (21% yield) of a clear, colorless liquid. Data of the mixture of isomers is as follows. TLC (silica gel, CH_2Cl_2) R_f=0.81. IR (film) 2960, 2940, 2880, 1460, 1380, 1280, 1205, 1020 cm^{-1}. ^{1}H-NMR (CCl_4) δ 0.8-1.0 (m, 9H), 1.0-2.2 (m, 16H), 4.00, 4.05 (4H). ^{13}C-NMR indicated a mixture of four products, the boronate ester resonances of which are as follows.[14] ($CDCl_3$) δ 65.9, 65.4, 65.2, 64.9. MS (70 eV) m/e 264 (7 rel. %), 221 (100), 151 (28). Elemental Analysis calculated 72.73% C, 11.06% H; found 73.00% C, 11.06% H. GC (5% SE-30, 140°, 6' x 1/8", v = 50 cm^3/min) integration gave four peaks of the following retention times and relative areas. t_R 4a 12 min. (25%), 4b 14 min. (31%), 4c 18.5 min. (43%), 4d 19.5 min. (1%).

High field ^{1}H-NMR of the four boronate ester obtained by preparative gas chromatography provided the following data: 4a 400 MHz ($CDCl_3$) δ isopropyl methyl doublets 0.861, 0.871 J = 6.5, 0.88, 0.86 J = 7.0, methyl doublet 0.93, 0.91 J = 7.0, boronate ester singlet 4.12; 4b 400 MHz ($CDCl_3$) δ methyl doublet 0.66, 0.67 J = 6.7, isopropyl doublets 0.80, 0.82 J = 6.1, 0.83, 0.85 J = 7.3, boronate ester singlet 4.14; 4c 400 MHz ($CDCl_3$ δ methyl doublet 0.84, 0.85, J = 6.4, methyl doublet 0.87, 0.89, J = 6.7, methyl doublet 0.91, 0.93 J = 7.0, boronate ester singlet 4.20; 4d 200 MHz ($CDCl_3$) δ singlets 0.82, 0.85, 0.86, 0.93, 0.89 (twice the area of the other singlets), boronate ester singlet 4.15.

6-Cadinyl-1,3,2-dioxaborole (4, R=CH_3)[16] to a stirred solution of THF (94 mls) and $H_3BS(CH_3)_2$ (10 M, 4.9 mls, 49 mmol) at -40° under N_2 atmosphere was added 5-(E)-2,6,10-trimethyl-1,5,9-undecatriene (1, 9.4 g, 48.9 mmol) in dry THF (20 mls) over 30 min. Stirring was continued for 1 hr at -30°, 1 hr at 0°, and overnight at room temperature.

The mixture was transferred by syringe to an autoclave under N_2 atmosphere and ethylene

glycol (8.7 g, 140 mmol, 3 eq, 7.8 mls) was added. The autoclave was pressurized with CO (1600 psi) and heated for 1 hr at 50°, then 24 hrs at 150°. After cooling to room temperature the mixture was added to hexane (150 mls), partitioned with H_2O (2 x 20 mls) and the organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Short path distillation (~118°, 0.35 mm) afforded a cloudy colorless liquid. Medium pressure liquid chromatography (silica gel, CH_2Cl_2) afforded 3.9 g (29% yield) of a clear, colorless liquid. Data of the mixture of isomers is as follows. TLC (silica gel, CH_2Cl_2) R_f = 0.90. IR (film) 2950, 2930, 2870, 1450, 1385, 1335, 1290, 1235, 1210, 1150, 1030, 950 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 0.8-1.0 (m, 12H), 1.0-2.0 (m, 15H), 4.0 and 4.1 (singlets, total 4H). ^{13}C-NMR ($CDCl_3$) indicated at least two boronate esters δ 65.2, 65.0[14]. GC (5% SE-30, 6' x 1/8", 150°, ν = 55 cm^3/min) broad peak 5.0 min.

Elemental analysis calculated 73.38% C, 11.23% H; found 73.70% C, 11.48% H. MS (70 eV) m/e 278 (7 rel.%), 235 (100) 165 (33). 200 MHz ^{1}H-NMR gave the following methyl resonances ($CDCl_3$) δ 0.69, 0.72, 0.76, 0.77, 0.79, 0.80, 0.83, 0.84, 0.81, 0.95, 0.98, 0.99. Boronate ester resonances occured at δ 4.03 and 4.09 (integral 1:2, respectively).

4-Desmethyl-6-cadinol (2, R=H) General procedure - to the boronate esters (previously isolated by preparative gas chromatography, 5% SE-30, 150°, 16' x 1/4", ν = 100 cm^3/min) in THF was added 5 M NaOH. Hydrogen peroxide (30%) was added slowly and the stirred mixture was refluxed. After cooling to room temperature the mixture was partitioned with hexane and the organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure, affording clear, colorless, liquids as per Table I.

Acknowledgements - We gratefully acknowledge NIH for support of this work (PHS Grant No. AM-18802).

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[10]All compounds are racemic, formulas indicate relative stereochemistry.

[11]Triene 1 (R-CH_3) reacts similarly. Although the cadinol series 2 (R=CH_3) was not separated by glc, 200 MHz ^{1}H-NMR indicates it may follow the same trend, based upon the methyl resonances of 4 (R=CH_3) and 4 (R=H).

[12]The β-attachment of double bond c to boron hydride II requires a more strained ring for reaching to the "α" face of double bond c, thus 3b should be favored over 3a.

[13]These attempts include multiple glc and lc chromatographic techniques, as well as derivatization.

[14]These boronate ester resonances were accompanied by the usual envelope of aliphatic resonances.

[15]Boron is assumed to be planar in all trivalent structures and in structures 4a and 4b only one chair-chair conformation is illustrated.

[16]A number of variations of the hydroboration process were used. The experimental section reports the one most frequently used.

Table I

Ester (weight)	THF(mls)	NaOH(mls)	H_2O_2(mls)	Reflux Time (hrs)	Product wt (mgs) of 2 and yield		
4a 59 mg (0.22 mmol)	3	0.12	0.10	6	2a	40	(87%)
4b 27 mg (0.10 mmol)	1	0.20	0.16	24	2b	19	(90%)
4c 145 mg (0.55 mmol)	8	0.22	0.20	6	2c	110	(96%)
4d 6.5 mg (0.025 mmol)	1	0.05	0.05	6	2d	5	(96%)