

HYDROBORATION AND DIIMIDE REDUCTION OF CARYOPHYLLENE AND ISOCARYOPHYLLENE

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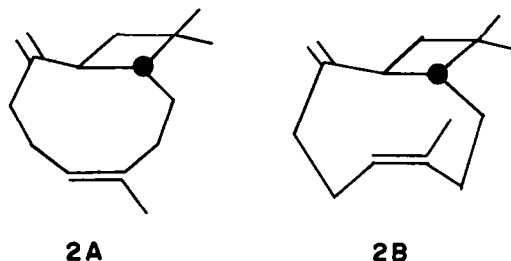
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Abstract—The monohydroboration of caryophyllene with dicyclohexylborane followed by oxidation brought about the participation of the (*E*)-trisubstituted double bond in preference to the exocyclic double bond during hydroboration to the corresponding unsaturated alcohol. This alcohol gave the corresponding ketone by oxidation. Isocaryophyllene under similar conditions provided the unsaturated alcohol as the major product, wherein the participation of the exocyclic double bond took place during hydroboration. Our attempts to achieve cyclic hydroboration with caryophyllene or isocaryophyllene using thexylborane resulted in the formation of the corresponding unsaturated alcohol. We achieved partial regioselective reduction of caryophyllene and isocaryophyllene with diimide to produce the corresponding dihydroderivative.

The unique structural features present in isomeric sesquiterpenes, caryophyllene (1) and isocaryophyllene (2)¹ have made them a rich source of interesting reactions. Our interest in the chemistry of nine-membered cyclic system² prompted us to examine the behaviour of 1 and 2 towards orangoboranes³ and diimide reagents.

Hydroboration involves a *cis*-anti-Markovnikov addition of the boron-hydrogen bond free from undesirable skeletal rearrangement of the substrate molecule.⁴ Partially alkylated boranes such as disiamyl borane and dicyclohexylborane permit greater regioselectivity as well as selectivity while carrying out monohydroboration of dienes. The monoalkylborane, thexylborane allows double hydroboration of certain dienes giving cyclic organoboranes. Diimide is a mild reducing agent,⁵ achieves *cis*-hydrogenation from the less hindered side of the double bond without any fear of isomerisation.

The molecular model of caryophyllene (1) indicates that the arrangement of 9-membered ring of 1 has the plane of the (*E*)-endocyclic double bond perpendicular to the plane of cyclobutane ring. There are two such conformers (1A and 1B), in each of which only one face of the π -bond is exposed to attack, the other side being completely shielded by the rest of the molecule. Consequently, each conformer can give rise to a single diastereoisomer by symmetrical reagents which add to this π -bond through a cyclic transition state with little or no ionic character. In isocaryophyllene (2), the (*Z*)-endocyclic double bond is less rigid and it has greater freedom to change from one extreme conformation to the other (2A \rightleftharpoons 2B), and both sides of the double bond are relatively accessible in 2A and 2B for attack by similar reagents.⁶ Therefore, such additions should lead to a mixture of diastereoisomers. The disposition of exocyclic double bond in caryophyllene conformers (1A and 1B) suggest that the α -side provides a less crowded environment for the double bond. Hence the approach of any reagent with steric requirement should be preferred from this side. On the other hand, the molecular models of isocaryophyllene conformers (2A and 2B) indicate less selectivity at the exocyclic double bond as compared to 1A and 1B.



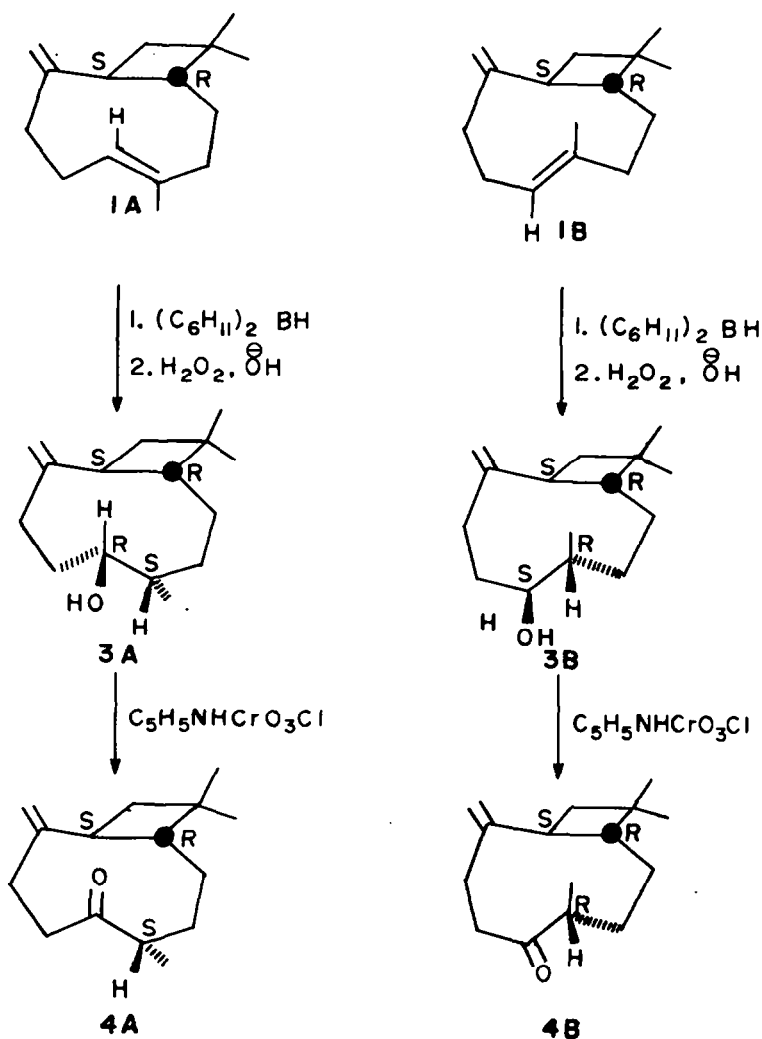
It appeared therefore appropriate to establish the selectivity of 1 and 2 towards monohydroboration reaction and partial diimide reduction. In the course of the study we were interested to establish the participation of stable conformers 1A and 1B towards hydroboration, and also transannular participation of both the double bonds in 1 or 2 towards cyclic hydroboration.

RESULTS

Hydroboration of caryophyllene (1) and isocaryophyllene (2)

Monohydroboration of caryophyllene (1) with dicyclohexylborane⁷ was studied varying the ratio of reactants in THF in order to find the optimum conditions for the formation of maximum quantity of monohydroboration product. When dicyclohexylborane and caryophyllene (1) were used in a 2:1 molar ratio, the amount of recovered caryophyllene (1) was a minimum and the yield of caryophyllene alcohol (3) was a maximum (70% yield) after usual alkaline oxidation of the intermediate organoborane (Scheme 1). Its IR spectrum shows absorptions at 1640 and 885 cm^{-1} characteristic of exocyclic methylene group and complete absence of absorptions at 1679 and 835 cm^{-1} due to endocyclic double bond. The NMR spectrum shows vinyl methylene protons at 4.87 δ as a singlet. Oxidation of caryophyllene alcohol (3) with pyridinium chlorochromate⁸ provided caryophyllene ketone (4) in good yield. Our attempt to achieve cyclic hydroboration of 1 with thexylborane⁹ resulted in the formation of only 3 after alkaline H_2O_2 oxidation.

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Scheme 1.

The hydroboration-oxidation of isocaryophyllene (2) with dicyclohexylborane⁷ yielded isocaryophyllene alcohol [(Z) - (1R, 9S) - 4,11,11 - trimethyl - 8 - hydroxymethylbicyclo(7.2.0)undecan - 4 - ene] (5) and diastereoisomeric [4,11,11 - trimethyl - 8 - methylene - bicyclo(7.2.0)undecan-5-ol] (6) (70% yield) in a ratio 4:1 as analysed by NMR (Scheme 2). However, pure isocaryophyllene alcohol (5) was obtained during hydroboration of 2 with tetrylborane⁹ followed by oxidation. Compound 5 had IR absorptions at 1670 and 840 cm⁻¹

showing the presence of $\begin{array}{c} \diagup \\ \text{C}=\text{C} \\ \diagdown \end{array}$. The NMR

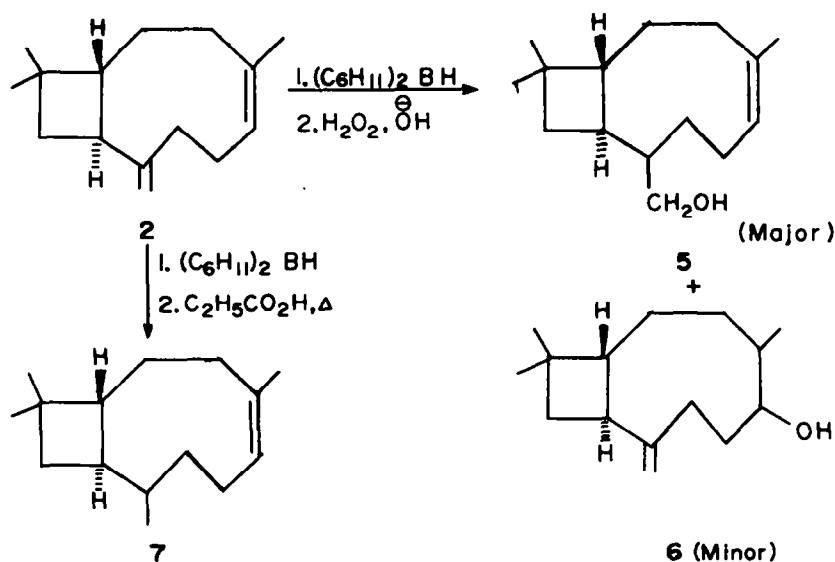
spectrum displays an olefinic proton at 5.0–5.5 δ as a triplet (J = 6.5 Hz) and OH proton at 2.77 δ as a singlet. Hydroboration and protonolysis¹⁰ of isocaryophyllene (2) yielded the dihydroisocaryophyllene (7) in 57% yield (Scheme 2).

The reducing agent diimide was generated *in situ* by oxidation of hydrazine with H₂O₂ in presence of cupric ions.¹¹ Partial reduction of caryophyllene (1) yielded dihydrocaryophyllene [(1R,9S)-4,11,11-trimethyl-8-methylenebicyclo(7.2.0)undecane] (8) with 100% conversion to the product in good yield (Scheme 3). Its IR reveals the presence of only exocyclic methylene group

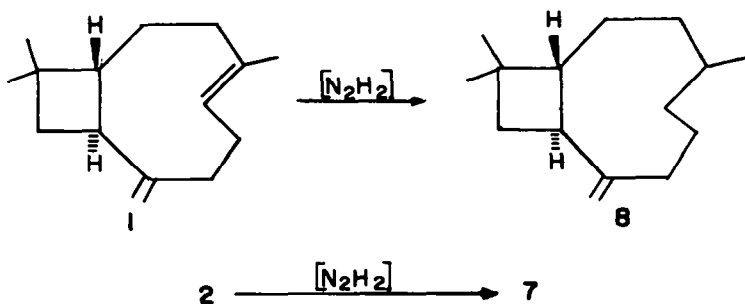
(3065, 1640 and 885 cm⁻¹). Its NMR shows two olefinic protons at 4.85 δ as a singlet. Isocaryophyllene (2) under similar conditions underwent conversion only to the extent of 80% to give dihydroisocaryophyllene (7) (Scheme 3) which was separated by preparative GLC and was identified as 7 (GLC retention times, IR and NMR).

DISCUSSION

Our results on the monohydroboration-oxidation of caryophyllene (1) conclusively point out that the more substituted (E)-double bond selectively participates during hydroboration to give satisfactory yield of caryophyllene alcohol (3). The selectivity as well as reactivity may be attributed to the strain in the (E)-double bond in a 9-membered ring⁷ which is in agreement with the result of Brown.³ Our experiments on the variation of molar ratio of 1 to dicyclohexylborane from 1:1 to 1:2 indicated the increase in the percentage conversion of 1. There was no contamination of the dihydroboration product in spite of 100% excess use of dicyclohexylborane indicating greater selectivity of the (E)-double bond over exocyclic double bond during hydroboration. This unsaturated alcohol (3) on oxidation with pyridinium chlorochromate⁸ gave unsaturated ketone (4) in good yield. The presence of two



Scheme 2.



Scheme 3.

singlets at 4.85 and 4.95 δ in the ratio of 3:1 for the olefinic protons in the NMR spectrum of the ketone 4 and the wide range in the m.p. of the DNP derivative seem to indicate the presence of two diastereoisomers 4A and 4B. Our attempts to separate the two diastereoisomers (4A and 4B) have been futile. It has been shown that caryophyllene (1) forms two (*E*)-epoxides on peracid epoxidation⁶ and hence the presence of two conformers 1A and 1B. Since the addition of B-H bond occurs from the less hindered side and the replacement of B by OH in the oxidation proceeds with retention of configuration,⁴ one would expect the formation of two diastereoisomeric unsaturated alcohols 3A [(1R,4S,5R,9S) - 4,11,11 - trimethyl - 8 - methylene - bicyclo(7.2.0)-undecan-5-ol] and 3B [(1R,4R,5S,9S)-4,11,11-trimethyl - 8 - methylene - bicyclo(7.2.0)undecan - 5 - ol] only when both the conformers of caryophyllene (1A and 1B) participate in the hydroboration reaction. Therefore, our results are completely in agreement with the findings of Warnhoff.⁶ Our attempts to achieve protonolysis of the intermediate organoborane from 1 resulted in the formation of a complex mixture of products. This may be attributed to the instability of the intermediate organoborane towards protonolytic conditions. Our attempt to achieve cyclic hydroboration of 1 using thexylborane gave only the monohydroboration product, 3 after oxidation. This suggests that the intermediate unsaturated organoborane is not in the vicinity of the exo-

cyclic double bond to achieve transannular addition of B-H bond across the ring in an intramolecular fashion.

The hydroboration of isocaryophyllene (2) with dicyclohexylborane followed by oxidation gave a mixture of unsaturated alcohols, 5 and 6 in a ratio 4:1. Although the reaction is not completely selective, the formation of 5 as the major product indicates greater selective attack of dicyclohexylborane at the disubstituted exocyclic double bond. However, we have been able to achieve complete selectivity using thexylborane during our attempt to achieve cyclic hydroboration which yielded only the unsaturated alcohol (5). Our spectral data on 5 do not allow us to define the exact configuration of C-8. The protonolysis study on the intermediates from 2 obtained using dicyclohexylborane provided only the dihydroisocaryophyllene (7) indicating the selective protonolysis of the major intermediate organoborane which contains primary carbon bond of isocaryophyllene moiety with boron.

Our results with partial reductions of 1 and 2 with diimide are in agreement with the expected behaviour of diimide. The complete reduction of caryophyllene (1) to dihydrocaryophyllene (8) and the selectivity observed may be attributed to the strain of the (*E*)-trisubstituted double bond in a 9-membered ring. The selectivity observed in the case of isocaryophyllene (2) is attributed to the preference in steric environment for reduction at the exocyclic double bond as compared to (*Z*)-trisubstituted endocyclic double bond. Thus the results are in

concurrence with the observed partial reduction with (*Z,E*)-1,5-cyclodecadiene¹² and terminal allenes.¹³

CONCLUSIONS

The results of this study fully support the earlier generalizations regarding the selectivity as well as reactivity of the monohydroboration reaction and partial diimide reduction of dienes containing two double bonds which differ either in substitution or/and configuration. Oxidation of the unsaturated alcohol (3) to the ketone (4) further establishes the presence of two conformers (1A and 1B) of caryophyllene (1). The present procedures provide convenient methods of preparing the unknown caryophyllene alcohol (3), caryophyllenone (4) isocaryophyllene alcohol (5) and dihydrocaryophyllene (8) for the first time.

EXPERIMENTAL

Materials. GLC was performed with a Varian Aerograph Model 90-P instrument. NMR and IR spectra were obtained with a Bruker WH-90 and Beckman IR-8 spectrometer, respectively. The b.ps were uncorrected.

Hydroboration of caryophyllene (1) with dicyclohexylborane. To 20 mmol of dicyclohexylborane a soln of caryophyllene (2.04 g, 10 mmol) in 20 ml THF was added at 0° and was stirred for 2 hr at 0° and additional 2 hr at room temp. The residual hydride was destroyed with 1:10 mixture of water and THF. Then it was oxidised using 3.2 ml of 3 N NaOH and 3.2 ml of 30% H₂O₂ in the usual manner. The mixture was extracted with ether, washed with water and brine, dried over MgSO₄. Solvent and cyclohexanol were removed under vacuum and the residue on chromatography over basic alumina gave 0.2 g of unreacted caryophyllene and 1.4 g (70% based on reacted caryophyllene) of caryophyllene alcohol, b.p. 140–142° (0.1 mm); IR(CCl₄): 3625, 3400, 3080, 1640, 1385, 1370, 1070 and 885 cm⁻¹; NMR(CDCl₃) δ ppm: 1.00(3H, s), 1.03 (6H, s), 3.5–3.7 (1H, m), 4.33 (1H, s) and 4.87 (2H, s). (Found: C, 80.72; H, 11.40. Calc. for C₁₅H₂₆O: C, 81.03; H, 11.71%).

Pyridinium chlorochromate oxidation of caryophyllene alcohol (3). A mixture of pyridinium chlorochromate (0.60 g, 2.8 mmol) and fused NaOAc (0.093 g, 1.1 mmol) was suspended in 5 ml of CH₂Cl₂ and caryophyllene alcohol (0.50 g, 2.2 mmol) was rapidly added at room temp. with magnetic stirring. After 2 hr of oxidation, the mixture was diluted with anhydrous ether, filtered through neutral alumina. The filtrate on concentration gave an oil which on molecular distillation yielded 0.36 g (72%) of caryophyllene ketone; b.p. 120–122° (0.2 mm); IR(CCl₄): 1715, 1640, 1385, 1370 and 885 cm⁻¹; NMR(CDCl₃) δ ppm: 4.95 and 4.85 (2H, s) and 0.90–2.50 (22H, m). (Found: C, 81.48; H, 10.73. Calc. for C₁₅H₂₄O: C, 81.81; H, 10.91%).

Hydroboration of isocaryophyllene (2) with dicyclohexylborane. Monohydroboration of isocaryophyllene (2.04 g, 10 mmol) with dicyclohexylborane (20 mmol) was carried out in a manner similar to that described above to obtain 0.2 g of unreacted isocaryophyllene and 1.3 g (65% based on reacted isocaryophyllene) of isocaryophyllene alcohol, b.p. 142–143° (0.1 mm); IR(CCl₄): 3650, 3400, 1640, 1385, 1370, 1030, 890, and 835 cm⁻¹; NMR(CDCl₃) δ ppm: 0.94 (s), 0.97 (s), 1.6 (d, J = 2.0 Hz), 5.0–5.5 (t, J = 6.5 Hz) and 4.7–5.0 (m). (Found: C, 80.72; H, 11.30. Calc. for C₁₅H₂₆O: C, 81.03; H, 11.71%).

Hydroboration of caryophyllene (1) with thexylborane. Thexylborane (20 ml, 0.5 M, 10 mmol) in THF and caryophyllene (2.04 g, 10 mmol) in 20 ml THF were added dropwise simultaneously into a flask containing 20 ml of THF at 0° with stirring over a period of 30 min. The mixture was stirred for an hr and then stirred at room temp. for an additional 2 hr. The usual oxidation of thexyl organoboranes using 3.2 ml of 6 N NaOH and 3.2 ml of 30% H₂O₂ followed by work-up procedure as already described provided 1.2 g of unreacted caryophyllene and 0.7 g of (76%) caryophyllene alcohol (3).

Hydroboration of isocaryophyllene (2) with thexylborane. Hydroboration of isocaryophyllene (2.03 g,

10 mmol) using thexylborane (20 ml, 0.5 M, 10 mmol) as described above followed by oxidation yielded 1.15 g of unreacted isocaryophyllene and 0.65 g (67%) of isocaryophyllene alcohol, b.p. 141–142° (0.1 mm); IR (CCl₄): 3650, 3400, 1670, 1385, 1370, 1040 and 840 cm⁻¹; NMR (CDCl₃) δ ppm: 0.94 (3H, s), 1.00 (3H, s), 1.70 (3H, s), 2.17 (1H, s), 3.1–3.7 (2H, d, J = 4.0 Hz) and 5.0–5.5 (1H, t, J = 6.5 Hz). (Found: C, 80.83; H, 11.43. Calc. for C₁₅H₂₆O: C, 81.03; H, 11.71%).

Hydroboration-protonolysis of isocaryophyllene (2). Hydroboration of isocaryophyllene (4.08 g, 20 mmol) in 40 ml of THF with dicyclohexylborane (40 mmol) was carried out as described previously. The unreacted isocaryophyllene (0.42 g) and THF were removed from the organoboranes under vacuum. The organoboranes were treated with 5 ml of propionic acid and refluxed for 8 hr. The mixture was cooled and sufficient 3 M NaOH added to ensure an excess. The mixture was then extracted with cyclohexane, washed with water several times till neutral, and dried over MgSO₄. Purification by filtering through a silica gel short column and distillation of the solvent yielded 2.1 g (57%) of dihydroisocaryophyllene, b.p. 110° (12 mm); IR (neat): 1670, 1385, 1370 and 835 cm⁻¹; NMR (CDCl₃) δ ppm: 0.94 (3H, s), 1.00 (3H, s), 1.66 (3H, d, J = 1.2 Hz) and 5.0–5.5 (1H, t, J = 7.5 Hz). (Found: C, 87.10; H, 12.58. Calc. for C₁₅H₂₆: C, 87.38; H, 12.62%).

Partial diimide reduction of caryophyllene (1). In a 250 ml 3-necked flask fitted with a gas outlet, a magnetic stirrer and a pressure-equalizing funnel, was placed a soln of caryophyllene (2.04 g, 10 mmol) in 60 ml of 95% EtOH. To this soln 98% hydrazine hydrate (2 g, 40 mmol) and 1 ml of 1% CuSO₄ aq were added. The flask with its contents kept stirred, was cooled by ice-salt mixture. The gas outlet was led into a water filled measuring cylinder to measure the volume of N₂ evolved. After allowing the system to attain steadiness 6 ml of 30% H₂O₂ was added from the dropping funnel at the rate of 5–6 drops per min. After no more N₂ evolved, water was added into the mixture, the product was extracted 3–4 times with *n*-hexane, and the combined extract, after washing with water, was dried over MgSO₄. Removal of solvent gave 1.8 g (87%) dihydrocaryophyllene, b.p. 110–112° (12 mm). IR (neat): 3065, 1640, 1385, 1370 and 885 cm⁻¹; NMR (CDCl₃) δ ppm: 0.95 (6H, s), 1.00 (3H, s) and 4.85 (2H, s). (Found: C, 87.10; H, 12.56. Calc. for C₁₅H₂₆: C, 87.38; H, 12.62%).

Partial diimide reduction of isocaryophyllene (2). Partial diimide reduction of isocaryophyllene (2.04 g, 10 mmol) as described above indicated 80% conversion into dihydroisocaryophyllene (98% GLC yield) as analysed by GLC. Pure dihydroisocaryophyllene was obtained by preparative GLC. (Found: C, 87.50; H, 12.85. Calc. for C₁₅H₂₆: C, 87.38; H, 12.62%).

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