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Studies on the Total Synthesis of the Saponaceolides. 2. Enantioselective Synthesis of 2-*epi*-Saponaceolide B

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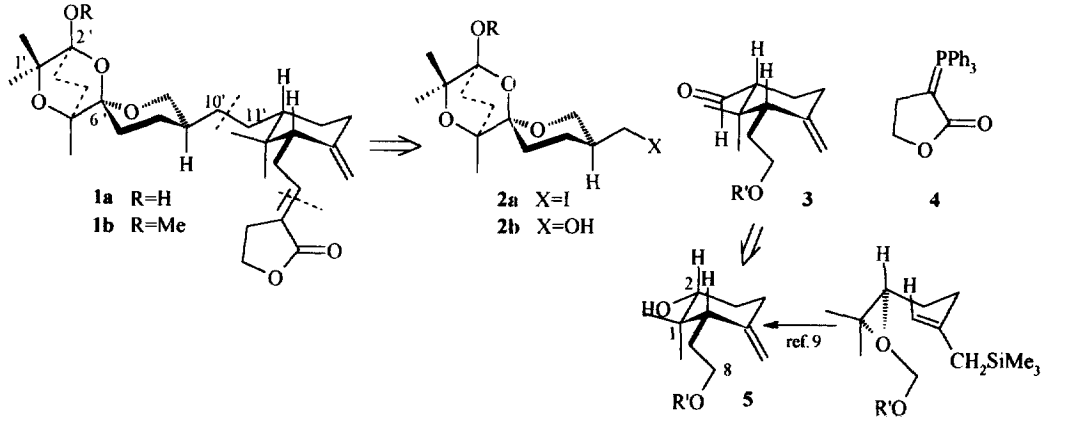
Abstract

The paper describes an asymmetric convergent synthesis of 2-*epi*-saponaceolide B, illustrating a general approach to the construction of the saponaceolide structure. The strategic C10'-C11' bond was formed by coupling a lithium salt containing the left part of the molecule with a carbonyl derivative representing the right part.

Keywords: Spiro compounds; Terpenoids; Fungi; Natural products

The promising antitumor activity and the unique structures of the saponaceolides [1-5] make these compounds of obvious synthetic interest; no total synthesis of the saponaceolides has appeared so far, though a few related synthetic studies have been published [5-7]. We envisioned a convergent approach to an enantioselective synthesis of saponaceolide B (**1a**), the most biologically active compound of this group [2,5], through a separate construction of three subunits **2a**, **3**, and **4**, and their subsequent coupling to assemble the entire saponaceolide structure. In the preceding Letter [8], we described a stereocontrolled route to the key building block **2a** representing the C1'-C10' segment of **1a**. Herein, we report an enantioselective



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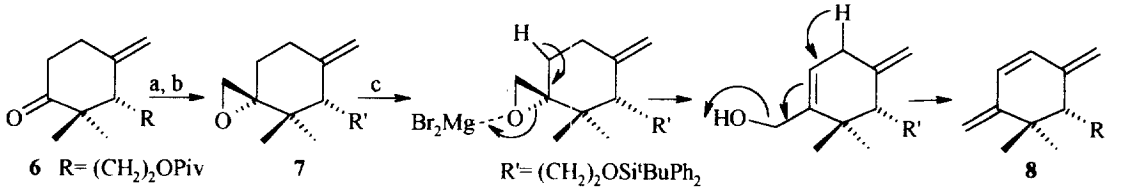
synthesis of the C1-C8 portion of saponaceolide B, to which the previously prepared subunit was joined in the crucial step of our synthetic project.

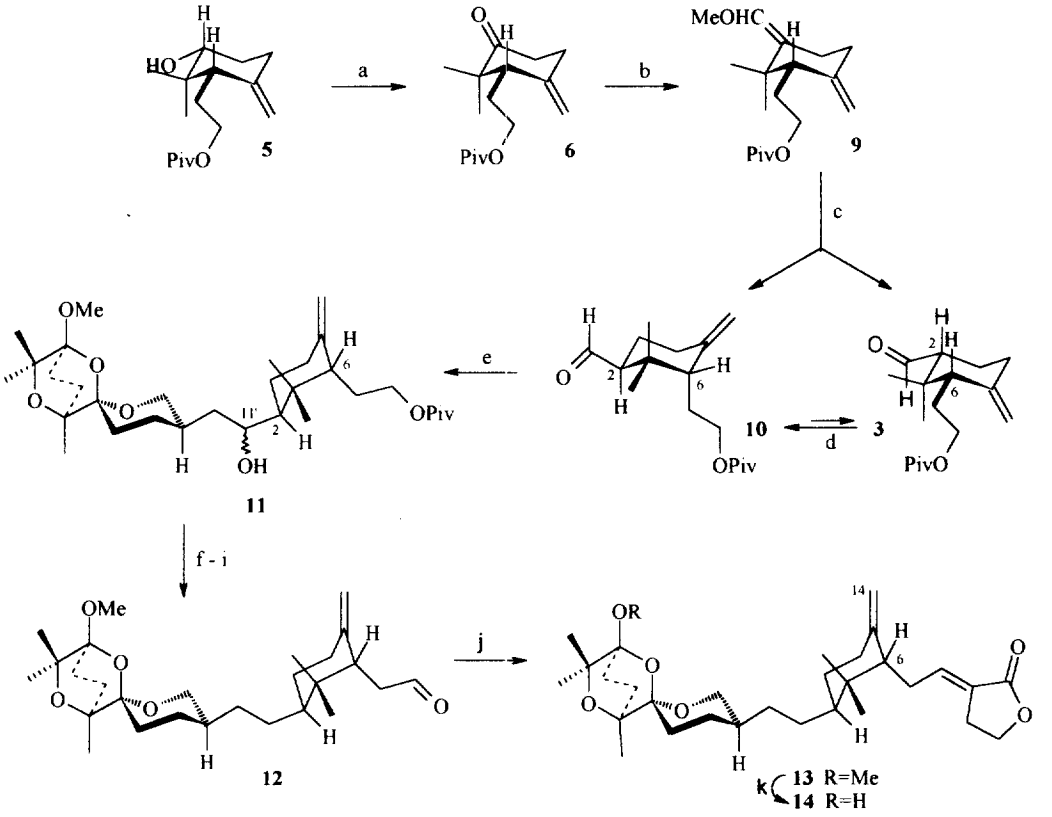
The synthetic challenge represented by the construction of the main fragment **3** with two asymmetric carbon atoms and a severely sterically congested 1,2,3-trisubstituted methylene-cyclohexane was initially addressed by attempting direct homologation of known alcohol **5**, ee 95% [9]. The Davis method [10] for the one step conversion of alcohols into the corresponding nitrile appeared particularly attractive, since this protocol was also applied to hindered alcohols. However, when **5** was submitted to the reaction mixture, namely NaCN (2eq.)-Me_3SiCl (2eq.) and cat. NaI in MeCN-DMF (1:1) at 60°C, the reaction did not proceed beyond the formation of the *O*-silyl ether of **5**, indicating that steric hindrance inhibited formation of the intermediate oxonium ion $[RO(SiMe_3)_2]I$ prior to the substitution by cyanide ion [10]. Alcohol **5** was then oxidised to the corresponding ketone **6** $[\alpha]_D^{20}$ –35.2 (c=1.5, CH_2Cl_2) with tetrapropyl ammonium perruthenate [11], anticipating that a sp^2 carbon would be more accessible than a sp^3 center. A large number of reagents [12] were thus examined for the homologation of **6**; however, the results of these reactions were disappointing, since **6** was either recovered unreacted or degraded under forced conditions. For example, ketone **6** was smoothly converted into epoxide **7**, $[\alpha]_D^{20}$ –23.4 (c=0.7, CH_2Cl_2) under modified Corey-Chaykovsky conditions [13]; however, the subsequent acid-catalysed rearrangement of **7** to the corresponding formyl derivative led to a mixture of products with BF_3 as catalyst, and afforded triene **8** [14] when $MgBr_2$ was employed instead. A possible mechanism of this rearrangement is shown in Scheme 1.



Scheme 1: a) Me_3SI (4eq.), *n*-BuLi (4eq.), THF, 0°C, 4h; b) $^tBuPh_2SiCl$ (1.1 eq.), cat. DMAP, imidazole (2 eq.), CH_2Cl_2, 0°C, 15 min, 95% from **6**; c) $MgBr_2$ (1.5 eq.), toluene, reflux, 2h, 70%.

Finally, following Corey's clever protocol [15] (Scheme 2), the long-sought formyl derivative of **6** was achieved in acceptable yield, however as a 1:1 mixture of separable C2 diastereomers **3**, $[\alpha]_D^{20}$ +7.45 (c=0.3, CH_2Cl_2) and **10**, $[\alpha]_D^{20}$ +23.1 (c=0.4, CH_2Cl_2). Upon exposure to MeONa in MeOH [16] this mixture became enriched in aldehyde **10** (**10**:**3**, 11:1). Though, in principle, each stereoisomer could be separately carried through the following steps, paucity of material forced us to continue our synthesis with the more abundant aldehyde **10**. Coupling of the left and right segments of saponaceolide B was thus accomplished *via* lithium-iodine exchange [17] of **2a** followed by addition of the anion to the carbonyl group of **10** [18].

Deoxygenation of the so produced secondary alcohol **11** (C11' configuration not assigned), followed by removal of the pivaloate group and oxidation of the primary alcohol led readily to aldehyde **12**. Wittig condensation of **12** with phosphorane **4** [19] smoothly afforded the unsaturated lactone **13**, thus completing the synthesis of the saponaceolide skeleton.



Scheme 2: a) cat. TPAP, 4-methylmorpholine N-oxide (6 eq.), 4Å MS, CH_2Cl_2, 20°C, 4h, 98%; b) Ph_2PCH_2OMe (6 eq.), *sec*-BuLi (6 eq.), THF, -95°C, 15 min, followed by **6**, -95°→ 20°C, 3h; then add MeOH and MeI (6 eq.), 20°C, 1h; c) 1.2N aq. HCl-THF (1:6), reflux, 30 min, **10** : **3**, 1:1; d) MeONa, MeOH, 20°C, 1h, **10** : **3**, 10:1; then chromatographic separation, 55% **10** from **6**; e) **2a** (1 eq.), *t*-BuLi (2.2 eq.), hexane-Et_2O (85.15), -78°C, 15 min, then add **10** (1 eq.) in Et_2O, -78°C, 1h, 50%; f) PhOCSCl (6 eq.), pyridine (20 eq.), CH_2Cl_2, 20°C, 30h, 100%; g) Bu_3SnH (5 eq.), cat. AIBN, THF, reflux,10h, 66%; h) $LiEt_3BH$ (3 eq.), THF, 0°C, 30 min, 70%; i) cat. TPAP, 4-methylmorpholine N-oxide (6 eq.), 4Å MS, CH_2Cl_2, 20°C, 1h, 95%; j) **4** (1.3 eq.), THF, 50°C, 20h, 90%; k) 10% aq. HCl, THF, 20°C, 5h, 70%.

Exposure of **13** to aqueous HCl readily afforded the free acetal **14**. Spectroscopic data of **14** and **13** were very similar with those of saponaceolide B (**1a**) [2,3] and its *O*-methyl acetal **1b**, respectively; however, in the ^{1}H-NMR spectrum of synthetic material **13** [20] the C14 olefinic protons and the geminal methyl groups at C1 were notably shifted in comparison with the

corresponding signals of **1b**. From these data it was clear that **14** was the 2-*epi*-isomer of saponaceolide B and that the C6 side chain in **13** was axially oriented and thus interacted with adjacent protons in a significantly different manner than in **1b**.

In conclusion, we have achieved the first enantioselective synthesis of two major segments **2** [8] and **3** of saponaceolide B (**1a**), and have set up a viable strategy for assembling the entire skeleton. Indeed, synthesis of **1a** simply requires coupling of the lithium reagent prepared from **2** with aldehyde **3** instead than with its stereoisomer **10**. Our progress in this field will be reported in due time.

Acknowledgements

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[14] Selected spectral data for the triene system: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.81 (t, J=1.5Hz,1H), 4.90 (d, J=2Hz, 1H), 4.94 (s, 1H), 4.95 (t, J=1.5 Hz, 1H), 5.93 (d, J=10 Hz, 1H), 6.0 (d, J=10 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 111.7 (CH_2), 113.7 (CH_2), 127.1 (CH), 135.4 (CH), 145.1 (C), 150.6 (C).

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[16] Stereochemistry of the two stereoisomers could not be assigned with confidence at that time, though molecular modelling indicated a major thermodynamic stability for the 2*S*,6*S*-stereoisomer in which the axially oriented C6 side chain relieves $A^{1,3}$ strain and one gauche interaction with the geminal dimethyl group.

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[18] The success of this lithiation reaction depended dramatically on the ratio between Et_2O and hexane in the solvent mixture. The amount of Et_2O must be kept at minimum to avoid formation of alcohol **2b**, possibly arising *via* this mechanism:

$$\text{EtOEt} \xrightarrow{t\text{-BuLi}} CH_2CH_2 + EtO^- \xrightarrow{RI} \text{ROEt} \xrightarrow{t\text{-BuLi}} \text{ROLi} + CH_2CH_2$$

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[20] Spectral data for compound **13**: ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.68 (s, 3H), 0.81 (s, 3H), 1.02 (s, 3H), 1.07 (s, 3H), 1.16 (s, 3H), 0.9-2.4 (m, 21H), 2.85 (m, 2H), 3.4 (s, 3H), 3.59 (ddd, J=11.0, 4.5, 2.0 Hz, 1H), 3.74 (t, J=11.0 Hz, 1H), 4.36 (t, J= 7.0 Hz, 2H), 4.57 (bs, 1H), 4.73 (bs, 1H), 6.66 (m, 1H). CIMS (NH_3) *m z:* 534 ($M+NH_4^+$), 516 (M^+).