Stereoselective Synthesis of (+)-Strictanonic Acid, the Enantiomer of a New Type of Diterpenoid, isolated from *Grindelia stricta* and *Chrysothamnus paniculatus*

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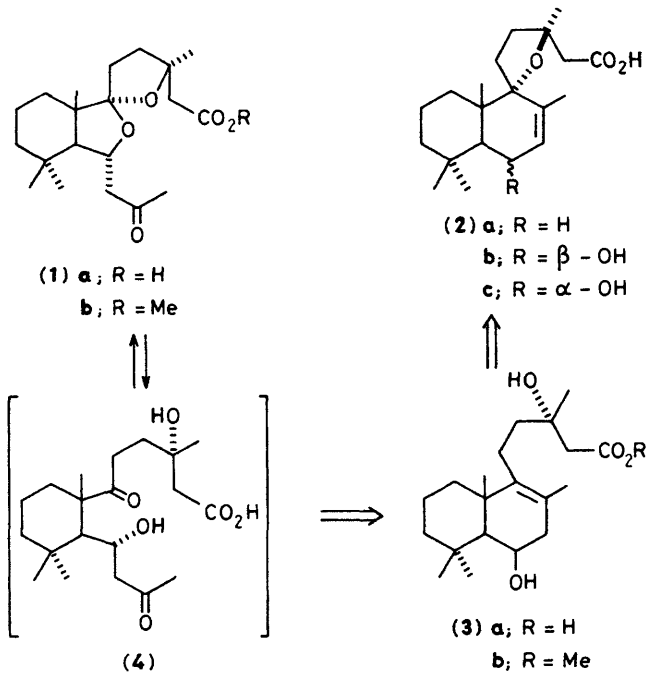
The synthesis of (+)-strictanonic acid (**1a**) from grindelic acid (**2a**) *via* the key intermediate (**3a**) is described; the synthesis confirms the proposed structure of (**1a**) and establishes its absolute stereochemistry.

A large number of diterpenes, structurally related to grindelic acid (**2a**), have been isolated from several *Grindelia* species and some of them showed interesting antifeeding properties.[1] More recently, a new type of diterpenoid (**1a**) was isolated by two groups, from *Grindelia stricta*[2] and *Chrysothamnus paniculatus*,[3] and named strictanonic acid and chrysothame respectively.

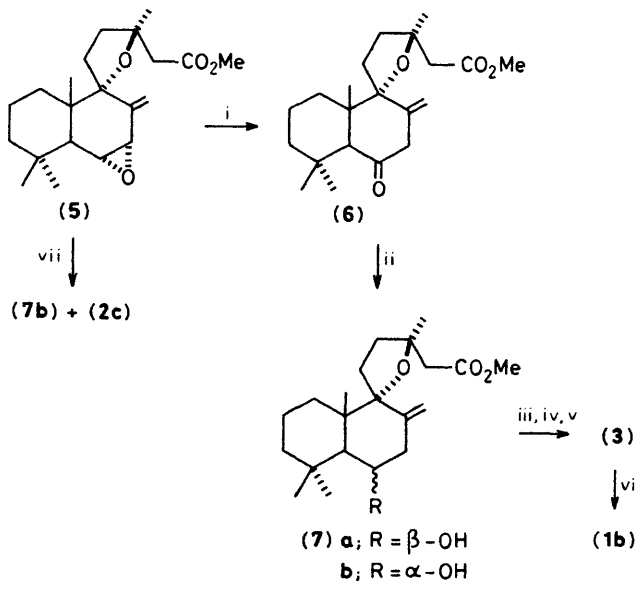
The proposed structure of (**1a**) was based on spectroscopic evidence and biogenetic considerations. The stereochemistry at C-6 and C-9 was suggested from the ^{1}H n.m.r. J_{5-6} (10.7 Hz) value, differences in the n.m.r. shifts of (**1a**) and (**1b**) for C-6 and C-7,[3] and the downfield shift of the C-5-H signal.[2]

In order to confirm the structure and stereochemistry we decided to synthesize (**1a**). Retrosynthetic analysis allowed us to establish a relation between (**1a**) and grindelic acid (**2a**) *via* the key intermediate (**3a**), which had the desired stereochemistry at four of the five chiral centres present in (**1a**), Scheme 1. Although we were moderately concerned about the stereochemical outcome of the impending spiroacetalization of (**4**), it seemed reasonable to assume that the stereocontrol in the acetalization would be dominated by the stereoelectronic effects[4] and, therefore, would produce the C-9 stereochemistry as in the natural product.

Based on our previous experience on the synthesis of other



Scheme 1



Scheme 2. i, $Et_2O \cdot BF_3$, toluene −20 °C, 2 min, then $NaHCO_3$–H_2O; ii, $Zn(BH_4)_2$, Et_2O, 18 °C, 30 h; iii, 1 M NaOH, dioxane–H_2O, 100 °C, 3 h; iv, NaH (2 equiv.), Et_2O, then Na in liq. NH_3; v, CH_2N_2–Et_2O, 0 °C; vi, O_3–Cl_2CH_2–MeOH, −40 °C, 30 min, then $(MeO)_3P$, vii, H_2–PtO_2, 1 atm.

natural products related to (**2a**),[5,6] we started from epoxide (**5**)† and the path followed is shown in Scheme 2.

Compound (**6**) was obtained almost quantitatively. Its stereospecific reduction however, turned out to be the most troublesome step of this strategy owing to the extremely high sensitivity of (**6**) to undergo isomerization to the α,β-enone. A reasonable yield (67%) of the desired β-alcohol (**7a**) together with a small amount (6%) of its C-6 epimer (**7b**)‡ was finally obtained by using $Zn(BH_4)_2$.[7] Hydrolysis of the ester function, followed by reductive opening (Na, liq. NH_3) of the tetrahydrofuran ring with simultaneous shift of the exocyclic double bond, produced the desired diol (**3a**) in *ca.* 80% yield, possessing all the required stereochemistry and structural features. Methylation with diazomethane followed finally by ozonolysis of (**3b**) and reductive work-up[8] produced a single compound whose spectroscopic characteristics were in agreement with those reported for (**1b**),§ except for the sign of its optical rotation. Since our starting material is of known absolute stereochemistry,[9] we conclude that the structure proposed for (**1b**)[2,3] is correct but the absolute stereochemistry is the enantiomeric one.

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† The preparation of compound (**5**), in four steps, starting from (**2a**) in *ca.* 60% overall yield is described in ref. 6. Satisfactory spectroscopic data were obtained for all compounds.

‡ The β-orientation of the hydroxy group in (**7a**), the major product in the reduction of (**6**), was firmly established by comparing its ^1H n.m.r. data with those of (**7b**), its C-6 epimer (described in ref. 6). Compound (**7a**) shows C-6-H as the X part of an ABXM system: C-7-H_α, C-7-H_β, C-6-H, and C-5-H, δ 4.31 (m, $w_{1/2}$ 13.0 Hz). Analysis of the ABX part shows $J_{7\beta-6}$ 3.51, $J_{7\alpha-6}$ 2.69, and $J_{7\alpha-7\beta}$ 13.5 Hz, corresponding to C-6-H equatorial. Compound (**7b**) in turn, shows C-6-H at δ 4.08 (ddd, $w_{1/2}$ 25.6 Hz, *J* 10.4, 8.8, and 6.4 Hz).

§ (+)-Strictanonic acid methyl ester (**1b**): [α] (lit.[2] values in parentheses) +4.6° (−7.6), 589 nm; +5.3 (−7.6), 578; +5.9 (−9.4), 546; +14.2 (−14.2), 436, in $CHCl_3$; i.r. (film): 3000—2850, 1740, 1720, 1450, 1360, 1240, 1105, 1030, and 880 cm^{-1}; ^1H n.m.r.: δ 0.92—0.99 (s, 9H, C-4- and C-10-Me), 1.20 (s, 3H, C-13-Me), 1.78 (d, 1H, *J* 10.0 Hz, C-5-H), 2.21 (s, 3H, C-8-Me), 2.68 (s, 2H, C-14-H), 2.71 (AB part of ABX, 2H, $\Delta\delta_{AB}$ 6.41 Hz, J_{AB} 15.8 Hz, C-7-H), 3.67 (s, 3H, OMe), and 4.3 (ddd, 1H, *J* 10.0, 10.0, 2.5 Hz, C-6-H); *m/z* 366.2405 (M^+, calc. 366.2406).

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