Absolute Stereochemistry of the Novel Dioxaspiro Diterpenoids Strictanonic and Grindelistrictic Acids. Stereoselective Synthesis of Strictanonic Acid Methyl Ester and its C-6 Epimer

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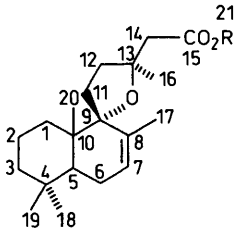
The stereoselective synthesis of (+)-strictanonic acid methyl ester (**2b**) and its C-6 epimer from a common chiral intermediate, derived from natural grindelic acid (**1a**) of known absolute configuration, is described. With the aid of one- and two-dimensional multipulse n.m.r. techniques, the complete stereochemistry of strictanonic acid and that of C-9 of the related bisnorditerpene grindelistrictic acid (**6a**) was established.

Most of the diterpenes isolated from plants of the genus *Grindelia* are structurally related to grindelic acid (**1a**).[1–4] Recently, a new type of terpenoid carrying a spiroacetal moiety, namely the diterpene strictanonic acid (**2a**)[5,6] and the bisnorditerpene grindelistrictic acid (**6a**)[5] were isolated, from natural sources, in very small amounts. Their structures were formulated mainly on the basis of spectroscopy. Therefore, unambiguous syntheses were needed for their confirmation. In addition, considerable attention has been given to natural products containing dioxaspiro moieties, due to both their biological and synthetic interest.[7–9] In this connection, we have already published some preliminary work.[10,11] We now present a complete report of the strategy that allowed us to synthesize the methyl ester (**2b**) of the natural spiro compound (**2a**), and the determination of the stereochemistry, including the absolute configurations, of both natural products, strictanonic and grindelistrictic acids (**2a**) and (**6a**).

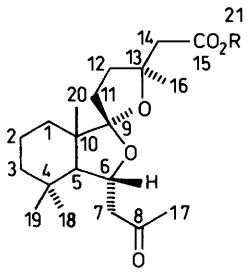
Although the structural relationship between (**2a**), (**6a**), and (**1a**) may not be so evident, a common carbon skeleton could be envisaged as shown by the numbering in the three structures. In addition, the proposed biogenetic route to (**2a**),[6] and our retrosynthetic analysis, shown in Scheme 1, both clearly lead to grindelic acid (**1a**). Therefore, in a critical analysis of the proposed structure for compound (**2a**), it would be reasonable to assume that the relative stereochemistry at C-5, C-10, and C-13, in the spirocompound, would be the same as in (**1a**). However, no justified assumptions can be made for the configurations at C-6 and C-9 and, considering the flexibility of a tetrahydrofuran ring, a large magnitude of $^3J(5/6)$ and small differences in the ^{13}C n.m.r. chemical shifts of compounds (**2a**) and (**2b**) are, in our opinion, not conclusive evidence in favour of a particular stereochemistry; therefore, all four isomeric structures (**2a**), (**3a**), (**4a**), and (**5a**) must be considered.

In our restrosynthetic analysis (Scheme 1), it is evident that the key intermediate would be compound (**7a**), which has the desired stereochemistry at four of the five chiral centres present in (**2a**). In addition, the outcome of the impending spiroacetalization of intermediate (**8**) would determine the C-9 stereochemistry in the very last step. Therefore, in order to have access to all aforesaid isomers of the natural strictanonic acid, we decided to carry out the synthesis of both C-6 epimers of (**7**): the acids (**7a**) and (**7c**).

The plan for the stereospecific synthesis of both epimeric homoallylic alcohols (**7a**) and (**7c**) is shown in Scheme 2. Both compounds could be obtained from a common chiral intermediate [epoxide (**9**)] which, in turn, derives from grindelic acid (**1a**). Epoxide (**9**) was prepared, in four steps in *ca.* 60% overall



(**1a**) R = H
(**1b**) R = Me



(**2a**) R = H
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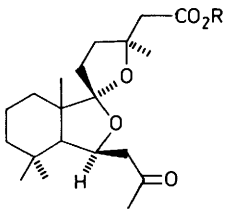

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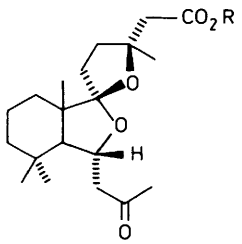
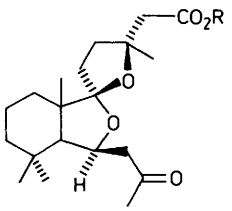
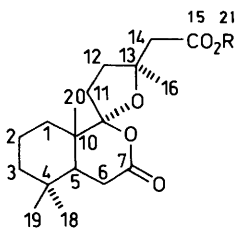


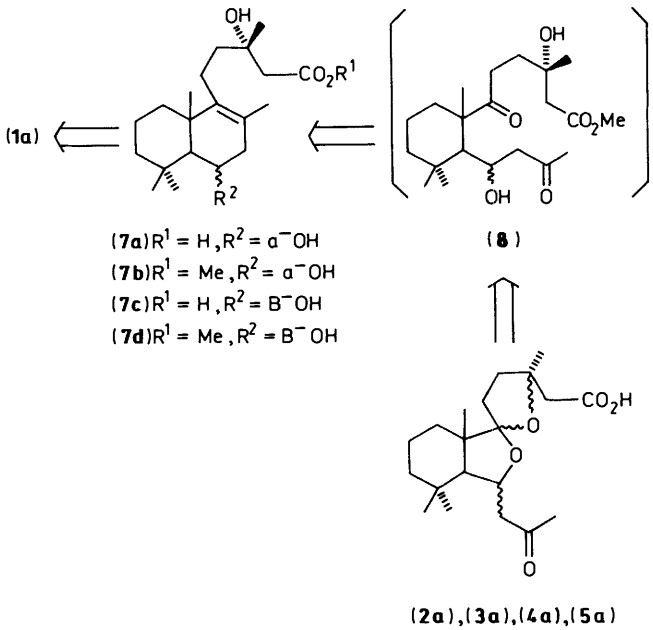
(**4a**) R = H
(**4b**) R = Me



(**5a**) R = H
(**5b**) R = Me



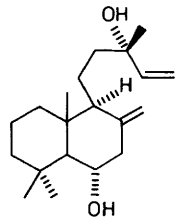
(**6a**) R = H
(**6b**) R = Me



Scheme 1.

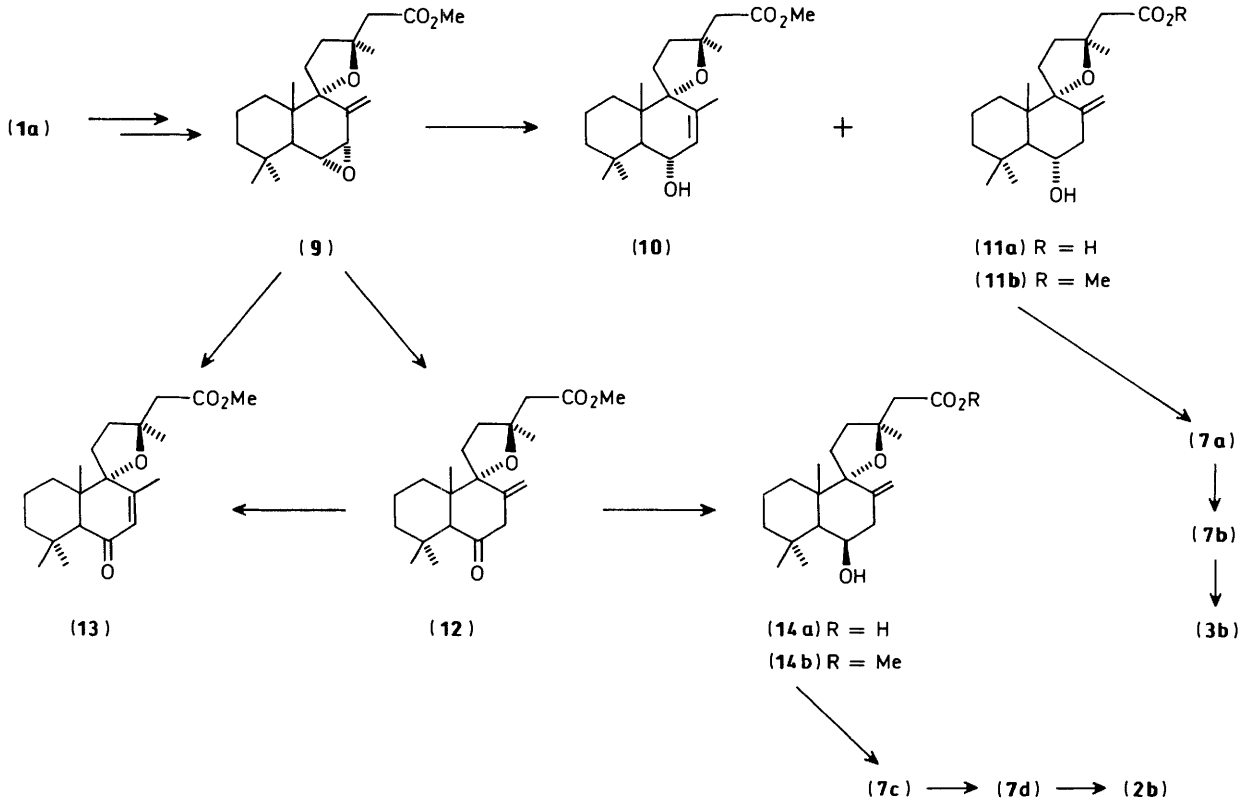
yield, as described in ref. 12. The reductive opening of the oxirane ring of (**9**), by catalytic hydrogenation,[13,14] was extensively studied. However, under the best conditions, the required ester (**11b**) was obtained in only 32% yield in a mixture where the isomer (**10**) was the main product.

The spectroscopic data obtained for compound (**10**) were in agreement with those reported in the literature[12,15] and establish as α the stereochemistry of the epoxide and the hydroxy groups of compounds (**9**) and (**11b**), respectively. In addition, the ^{1}H n.m.r. spectrum of (**11b**) shows two broad singlets at δ 4.75 and 4.86 assigned to the exocyclic methylene. The 6-H signal appears at δ 3.75 as a doublet of triplets (*J* 10.0 and 6.0 Hz) in agreement with the data reported for larixol (**15**).[16]



For the preparation of the epimeric alcohol (**14b**), we used a boron trifluoride–diethyl ether rearrangement of epoxide (**9**), at low temperature (−20 °C), to obtain ketone (**12**)[17,18] quantitatively. Compound (**12**) shows ^{1}H n.m.r. signals at δ 2.76 (s, 5-H), 2.81 (d, *J* 13.6 Hz, 7α-H), 3.66 (br d, *J* 13.6, 7β-H), and 4.83 (dd, 17-H_2, exocyclic methylene). The ^{13}C n.m.r. signal at δ_C 208.7 is characteristic of an unconjugated ketone.[19] The extreme sensitivity of ketone (**12**) to undergo isomerization to the α,β-enone (**13**) was the major difficulty found when attempting its reduction to the homoallylic alcohol (**14b**). Thus, most of the standard reducing methods[20–23] failed to produce the desired alcohol. Finally, the use of zinc borohydride[24] in ether afforded a 59% yield of the homoallylic alcohol (**14b**) together with a small amount (5%) of its C-6 epimer (**11b**), which could be separated by column chromatography.

The axial orientation of the C-6 hydroxy group in (**14b**) is in agreement with the ^{1}H n.m.r. data. The signal at δ 4.31, assigned to 6-H, appears as a multiplet ($w_{\frac{1}{2}}$ 13.0 Hz), as the X part of an



Scheme 2.

ABXM system integrated with 5-H and both C-7 hydrogens. Analysis of the ABX part, carried out by specific irradiations, showed that the $^3J(6/7\alpha)$ and $^3J(6/7\beta)$ values are 2.7 and 3.5 Hz, respectively. These small values ($J_{a,e}$ and $J_{e,e}$) are consistent only with a β orientation of the hydroxy group.

The opening of the tetrahydrofuran ring was performed on the carboxylic acids (**11a**) and (**14a**) by a sodium in liquid ammonia reduction and the reduced compounds were isolated as their methyl esters (**7b**) and (**7d**), respectively.

The proposed structures for the products (**7b**) and (**7d**) are supported by strong ^1H and ^{13}C n.m.r. spectral data. The lack of olefinic proton resonances and the appearance, in the spectra of both compounds, of broad singlets for allylic methyls (8-Me) at δ 1.57 and 1.60, respectively, and the pairs of olefinic carbon signals at δ_C 123.8, 139.8, and 121.7, 139.4, respectively, are indicative of the tetrasubstituted C-8/C-9 double bonds. In addition, the existence for each compound of only one quaternary carbon bearing oxygen, with signals at δ_C 70.9 and 71.0 respectively, is a clear indication of the opening of the tetrahydrofuran ring.

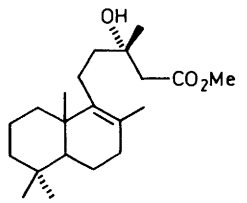
Again, the multiplicity of the ^1H n.m.r. signals, unequivocally assigned to 6-H in (**7b**) (δ 4.08, ddd, *J* 10,4, 8.8, and 6.4 Hz) and in (**7d**) (δ 4.43, br d, $w_{\frac{1}{2}}$ 9.5 Hz), confirms the stereochemistry of the C-6 hydroxy groups in both compounds.

The final step in our synthetic scheme requires the cleavage of the tetrasubstituted double bond to produce the intermediate diketone (**8**). Several procedures using osmium tetraoxide[25,26] and sodium periodiate[27,28] produced no or very poor yields.[29] Therefore, we explored the use of ozone[26,30] followed by a reductive work-up. The best conditions for this cleavage were found by using compound (**16**)[31,32] as a model compound. Compound (**16**) was obtained from (**1a**) in 67% yield. The best yields of the corresponding diketone (**17**) were produced at low temperature (−40 °C), in a 1:1 mixture of methanol–dichloromethane with trimethyl phosphite as reducing agent. When applied to substrates (**7b**) and (**7d**), ozonolysis produced, in each case, *single products*, (**3b**) and (**2b**) respectively, in better than 80% yield.

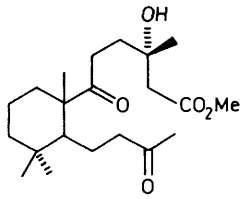
The spectroscopic data found for (**2b**), including its c.d. spectra,* are in total agreement with those reported for the methyl ester of the natural strictanonic acid.[5,6] It is worthwhile mentioning, however, as it had been expected that the $^3J(5/6)$ values are very similar in both C-6 epimers, and therefore cannot be used as conclusive evidence to establish the stereochemistry at C-6 of the natural product.

In order better to compare the physical data of synthetic (**2a**) with those of the crystalline natural carboxylic acid,[6] in particular its optical rotation, we attempted the saponification of both synthetic esters (**2b**) and (**3b**), by the standard procedure used for (**11b**) and (**14b**). Surprisingly, however, an unexpected acid, isolated as its methyl ester (**18**), was obtained (in better than 80% yield) from both reactions.

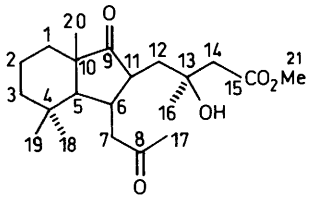
The formation of compound (**18**) upon alkaline treatment of (**2b**) or (**3b**) could be explained through a mechanism that implies the abstraction of one of the C-7 hydrogens with opening of the spiroacetal moiety, followed by an intramolecular Michael addition. The stereochemistry at C-5, C-10, and C-13 in ester (**18**) is assumed to be the same as in (**2b**). The configuration at C-6 and C-11 can be deduced as follows: the coupling constants $^3J(5/6)$ and $^3J(6/11)$ are 11.8 and 9.5 Hz, respectively



(**16**)



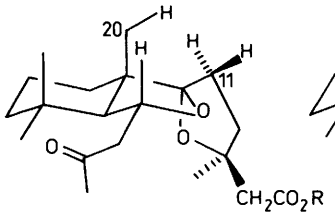
(**17**)



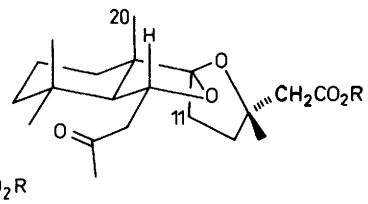
(**18**)

(Table 1), indicating an antiperiplanar orientation of both 5-H and 11-H with respect to 6-H. In addition the enhancements observed at 6-H upon irradiation of either of two methyls 4β-Me or 10-Me, confirmed its β orientation and, since n.O.e. effects were observed at the 5-H signal when irradiating 11-H, both hydrogens must be on the same face of the ring system. A complete assignment of the ^1H n.m.r. spectrum of compound (**18**) is shown in Table 1. The carbon shifts of the compounds discussed are listed in Table 4.

Through the synthetic sequence leading to (**2b**) (Scheme 2), we have secured the stereochemistry of four chiral centres: C-5, C-6, C-10, and C-13. Unfortunately, we have no control over the stereochemistry at C-9, resulting from the acetalization; therefore, two alternative structures [(**2b**) and (**4b**)] could be produced at this last step (Figure 1).



(**2b**)



(**4b**)

Figure 1.

In addition to the arguments supporting the proposed stereochemistry for natural strictanonic acid (**2a**), given in ref. 5 and 6, the fact that *only one spirocompound* is formed following the ozonolysis of (**7d**) strongly suggests that stereocontrol in the acetalization would be dominated by stereoelectronic effects[33] leading to the thermodynamically more stable compound which, as in many natural products possessing a dioxaspiro moiety, would show the double anomeric effect,[34,35] shown in structure (**2b**) (Figure 1). However, it would be convenient to look for stronger experimental evidence in order to differentiate between the alternative structures (**2b**) and (**4b**). Consideration of molecular models shows that only in structure (**2b**), owing to spatial proximity between 10-Me and the C-11 methylene, should we expect enhancement of the latter hydrogen signals, upon irradiation of the 10-Me, in a nuclear Overhauser enhancement[36–38] (n.O.e.) experiment. Such an observation would be strong evidence supporting structure (**2b**). Therefore, a

* A discrepancy found in the sign of the optical rotation led us to believe that we had synthesized the enantiomer of the natural product.[10] However, later on, a comparison of the c.d. curves, carried out by Professor Bohlmann, showed that both compounds have the same absolute configuration. The difference found was probably due to an error in the measurement, because of its low value and the small amount of the natural sample available.

Table 1. ^{1}H N.m.r. (400 MHz) spectral data of compounds (**2b**), (**3b**), (**18**), and (**6b**)

	(**2b**)				(**3b**)				(**18**)				(**6b**)			
	δ	Conf.[a]	Mult.	*J*(Hz)	δ	Conf.[a]	Mult.	*J*(Hz)	δ	Conf.[a]	Mult.	*J*(Hz)	δ	Conf.[a]	Mult.	*J*(Hz)
1-H_2	1.24	e	br dt		1.25	e	br dt									
	1.44	a	br td		1.50	a	br td									
2-H_2	1.5—1.6 overlapping m				1.5—1.6 overlapping m				1.6—1.75 overlapping m				1.5—1.65 overlapping m			
3-H_2	1.13	a	br td		1.15	a	br td		1.14	a	br td		1.20	a	br td	
	1.35	e	br dt		1.36	e	br dt		1.36	e	br dt		1.45	e	bt dt	
5-H	1.75	a	d	10.56	2.26	a	d	8.91	1.43	a	d	11.76	2.12	a	dd	6.3/12.6
6-$H_{(2)}$	4.26		ddd	10.6/3.8/9.5	4.51		ddd	8.9/3.2/11.7	2.34		dddd	11.8/9.5/3.2/5.8	2.35	a	dd	18.5/12.6
													2.56	e	dd	18.5/6.3
7-H_2	2.64		dd	3.8/15.6	2.51		dd	13.8/3.2	2.82		dd	19.4/3.2				
	2.74		dd	9.5/15.6	2.76		dd	13.8/11.7	2.92		dd	19.4/5.8				
									2.29		br dt	9.5/9.7/2.9				
11-$H_{(2)}$	1.75—1.85 overlapping m				1.60—1.80 overlapping m								2.05 overlapping m			
12-H_2	2.08		ddd		2.18		ddd		1.62		dd	14.6/9.5	1.87		ddd	12.0/10.9/3.4
									1.90		dd	14.6/2.9	2.36		ddd	12.0/9.0/6.3
14-H_2	2.62		d	14.2	2.63		br s		2.52		d	15.3	2.70		br s	
	2.66		d	14.2					2.56		d	15.3				
13-Me	1.17		s		1.19		s		1.24		s		1.30		s	
8-Me	2.19		s		2.20		s		2.13		s					
4α-Me	0.89	e	s		0.98	e	s		0.87	e	s		0.85	e	s	
4β-Me	0.95	a	s		1.02	a	s		0.96	a	s		0.87	a	s	
10-Me	0.96	a	s		1.09	a	s		1.00	a	s		1.00	a	s	
CO_2Me	3.64		s		3.62		s		3.66		s		3.60		s	

[a] Configuration: a = axial, e = equatorial.

Table 2. Connectivities established by n.O.e. difference experiments for compound (**2b**)

Proton irradiated	δ	Protons appearing in diff. spectrum
(4β-Me; 10-Me)[a]	0.95	6-H; 1-H^U; (2-H; 2-H);[b] 3-H^D; (11-H; 11-H; 12-H^U)[b]
4α-Me	0.89	3-H^D; 5-H; 3-H^U; 7-H^U; 7-H^D; 4β-Me
(13-Me)[c]	1.17	(12-H^U; 11-H; 11-H);[b] 14-H^U; 14-H^D; 1-H^D; 3-H^D
12-H^D	2.08	(12-H^U; 11-H; 11-H);[b] 14-H^U; 14-H^D

[a] Irradiated together due to signal proximity. [b] Too close to be easily distinguished. [c] Irradiation also affects 1-H^U and 3-H^U; [U] Upfield signal; [D] Downfield signal.

Table 3. Connectivities established by n.O.e. difference experiments for compound (**6b**)

Proton irradiated	δ	Protons appearing in diff. spectrum
(4α-Me)[a]	0.85	6-H^D; 5-H; 3-H^D; (6-H^U)[b]
(4β-Me)[a]	0.87	6-H^U; 3-H^D; 2-H; (5-H);[b] 4α-Me
10-Me	1.00	6-H^U; (11-H; 11-H);[c] 2-H; 1-H; 4β-Me
(12-H^U)[d]	1.87	12-H^D; 13-Me
6-H^D	2.56	5-H; 6-H^U; 4α-Me

[a] Partially irradiated together. [b] Low-intensity signals. [c] Too close to be easily distinguished. [d] Irradiation also affects 11-H; [U] Upfield signal; [D] Downfield signal.

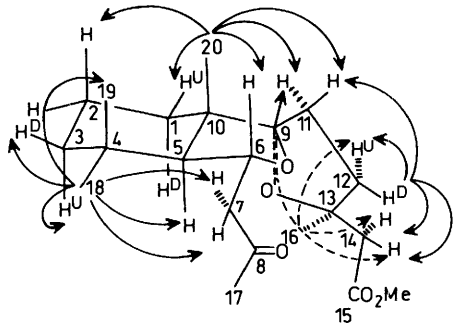


Figure 2. Relative stereochemistry of compound (**2b**) and proton–proton through-space connectivities, obtained by n.O.e. difference experiments

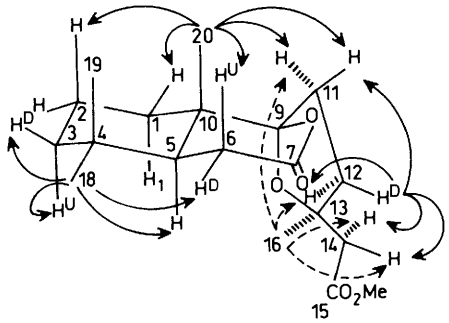


Figure 3. Relative stereochemistry of compound (**6b**) and proton–proton through-space connectivities, obtained by n.O.e. difference experiments

complete spectroscopic analysis using one- and two-dimensional n.m.r. techniques, and a series of n.O.e. difference experiments, were carried out on synthetic (**2b**) in order to assign unequivocally its ^{1}H n.m.r. spectrum and also to obtain conformational and configurational information. The results are summarized in Tables 1 and 2 and are shown schematically in Figure 2.

Table 4. ^{13}C N.m.r. chemical shifts of compounds studied

Carbon	(2b)	(3b)	(6b)	(11b)	(12)	(14b)	(7b)	(7d)	(18)	(16)
C-1	30.9	33.4	32.3	32.5	31.3	34.0	37.3	39.7	32.4	36.9
C-2	19.2	19.3	18.0	18.9	18.4	19.2	18.7	19.0	18.5	18.9
C-3	41.7	43.0	40.8	43.4	42.2	43.5	41.7	41.6	42.4	41.9
C-4	32.5	32.7	32.4	33.7	32.2	34.4	33.4	33.8	34.6	33.5
C-5	56.9	53.2	40.7	51.9	58.6	49.8	57.1	53.7	55.6	51.7
C-6	73.2	74.0	31.2	71.2	208.7	69.1	68.4	65.6	36.7	21.9
C-7	52.3	48.3	170.8	44.3	51.9	42.5	44.8	43.7	44.9	33.5
C-8	208.1	208.0		148.0	146.2	146.4	123.8	121.7	207.8	125.7
C-9	117.3	117.5	118.4	90.1	90.1	91.2	139.8	139.4	224.8	139.7
C-10	46.2	45.0	38.3	41.9	43.8	42.5	41.8	38.7	50.2	39.0
C-11	30.5	30.9	28.8	27.0	25.3	25.3	21.8	21.7	50.0	18.9
C-12	35.0	35.4	34.8	37.7	39.9	36.5	43.5	42.9	41.5	41.7
C-13	81.2	81.1	84.3	81.2	81.8	81.4	70.9	71.0	70.2	71.0
C-14	47.8	47.4	46.9	46.5	46.4	46.8	44.3	44.3	44.9	44.3
C-15	171.3	171.4	171.8	171.6	171.2	171.5	173.1	173.0	172.1	173.2
C-16	25.8	26.3	25.7	25.4	26.9	27.0	26.2	26.2	27.9	26.3
C-17	30.8	30.5		108.3	109.4	110.2	21.1	21.2	30.4	20.0
C-18	34.0	32.5	31.9	36.5	32.5	33.4	36.3	33.4	33.1	33.1
C-19	22.0	22.9	20.7	22.4	21.5	24.0	22.0	23.6	21.7	21.5
C-20	17.9	19.2	16.2	18.5	19.3	20.4	18.7	19.3	17.5	19.2
C-21	51.3	51.1	51.3	51.2	51.2	51.2	51.4	51.3	51.3	51.3

The complete ^1H chemical shift and stereochemistry assignments for (**2b**) are based on the following evidence. Irradiation at the 13-Me gave enhancements of both the C-14 methylene and the signals at δ 1.75—1.85, corresponding to the C-11 and C-12^U hydrogens. No n.O.e. was observed for the signal at δ 2.08. On the other hand, irradiation at δ 2.08 enhanced the signals at δ 1.75—1.85 and those of the C-14 methylene. Therefore, we assign the signal at δ 2.08 to 12-H^D with the stereochemistry as in Figure 2.

Irradiation at δ 0.89 (4α-Me) gave n.O.e. in signals at δ 0.95 (4β-Me), 2.64 and 2.74 (C-7 methylene), 1.75 (5-H), and 1.13 and 1.35 (C-3 methylene). Finally, when both (10 and 4β) angular methyls were irradiated together, enhancements were produced at the signal of 6-H, and at δ 1.35, 1.24, and 1.5—1.6 that allowed us to assign them to the 3-H, 1-H and/or 2-H, respectively. The observed n.O.e. of the signals at δ 1.75—1.85 (C-11 methylene) clearly showed the through-space relation expected for structure (**2b**), and therefore confirms the proposed stereochemistry at C-9.

A similar analysis was carried out for the methyl ester (**6b**) of grindelistrictic acid (**6a**), obtained from (**1a**), as described in ref. 11. The complete assignment of its ^1H n.m.r. spectrum is shown in Table 1. The results of the n.O.e. difference experiments, listed in Table 3, are shown schematically in Figure 3. The enhancements observed at 11-H (δ 2.05) and 6-H (δ 2.35) upon irradiation at the 10-Me (δ 1.00) were consistent with the stereochemistry proposed for C-9.[5,11]

In conclusion, the present study describes the stereospecific syntheses of both C-6 epimeric methyl esters of the novel diterpene strictanonic acid (**2a**), possessing the dioxaspiro moiety, and through this synthesis the structure was correlated with that of grindelic acid (**1a**), of known absolute configuration.[3,9] Therefore, the absolute stereochemistry of four of the five chiral centres (C-5, C-6, C-10, and C-13) of the acid (**2a**) was established and extensive n.m.r. analysis employing one- and two-dimensional techniques provided additional information to confirm the stereochemistry of C-9 in both (**2a**) and grindelistrictic acid (**6a**).

* The *J*-values are approximate due to partial overlap with the OMe signal.

Experimental

M.p.s were determined on an Ernst Leitz hot-stage apparatus and are uncorrected. I.r. spectra were recorded on a Beckman Acculab 8 spectrometer as solids in KBr disks unless specified otherwise. Most n.m.r. spectra were recorded on a Bruker WP 80 SY spectrometer for deuteriochloroform solutions with tetramethylsilane as internal standard. The ^1H n.m.r. spectra were recorded at 80.13 MHz and the ^{13}C n.m.r. spectra at 20.15 MHz. High-field measurements and 2D experiments were recorded on a Bruker AM 300, 400, or 500 as specified in deuteriochloroform solutions. For the 2D COSY and n.O.e. experiments Bruker standard software was employed. Column chromatography was performed on silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of ethyl acetate in hexane as solvent. Ether refers to diethyl ether. The homogeneity of all intermediates prior to the high-resolution mass spectral determinations was carefully verified by t.l.c., using the following solvent systems: hexane–ethyl acetate (7:3), chloroform–methanol (9:1), and cyclohexane–ether (6:4) on Merck aluminium plates precoated with silica gel 60 F-254 (0.2 mm).

Alcohol (**11b**).[12]—To a solution of the epoxide (**9**)[12] (150 mg, 0.43 mmol) in 95% ethanol (15 ml) was added platinum(IV) oxide (30 mg) and the mixture was stirred under hydrogen for 4 h. The catalyst was then removed by filtration through a Celite pad. The filtrate was evaporated under reduced pressure and the crude product (145 mg) was purified by column chromatography to afford the alcohol (**11b**) (48 mg, 32%) and the allylic isomer (**10**) (85 mg, 56%). Compound (**11b**) was an oil; $[\alpha]_D$ +12.6° (*c* 3.6 in $CHCl_3$); $\nu_{max.}$ 3 450, 3 100, 3 000—2 880, 1 750, 1 650, 1 450, 1 390, 1 350, 1 325, 1 260, 1 240, 1 105, 1 020, and 905 cm^{-1}; δ_H 0.76 (3 H, s), 0.99 (3 H, s), 1.17 (3 H, s), 1.30 (3 H, s, 13-Me), 2.52 (4 H, br s, 7- and 14-H), 3.65 (OMe), 3.75 (1 H, dt, *J* 10 and 6 Hz, 6-H),* 4.75 (1 H, br s, 17-H), and 4.86 (1 H, br s, 17-H); *m/z* 350 (M^+, 23%), 332 (10), 321 (6), 317 (4), 277 (4), 225 (23), 217 (9), 198 (28), 197 (100), 165 (34), 155 (23), 123 (41), 95 (38), 81 (18), and 69 (6) (Found: M^+, 350.2465. Calc. for $C_{21}H_{34}O_4$: *M*, 350.2457).

Hydroxy Ester (**16**).—A solution of compound (**1a**) (100 mg, 0.31 mmol) in anhydrous ether (15 ml) was treated with sodium

hydride (55%; 15.7 mg) under nitrogen and was stirred for 30 min at room temperature. The resulting suspension was cooled (−78 °C), ammonia (15 ml) was then condensed into the mixture, and sodium (35.7 mg, 1.55 mmol) was added under a stream of nitrogen. The mixture was refluxed for 4 h, and then t-butyl alcohol (0.1 ml) was added, the ammonia was allowed to evaporate off, and the residue was taken up in water (15 ml). The mixture was brought to pH 3 (10% hydrochloric acid) and then extracted with ether (3 × 10 ml). The combined extract was washed with brine, until neutral, and dried. The filtered solution was cooled (0 °C) and treated with an excess of an ethereal solution of diazomethane. The excess of diazomethane was destroyed (acetic acid) and the solvent was evaporated off. The residue was purified by column chromatography to afford the ester (**1b**) (10 mg, 0.03 mmol) and compound (**16**) (70 mg, 67%). Hydroxy ester (**16**) was an oil that showed spectral data coincident with those previously described.[32]

Ozonolysis of Hydroxy Ester (**16**).—A stream of ozonized oxygen was bubbled through a cold (−40 °C) solution of compound (**16**)[28,29] (30 mg, 0.09 mmol) in a 1:1 mixture of dichloromethane–methanol (6 ml) during 45 min. The excess of ozone was then displaced by a nitrogen stream, and the mixture was treated with trimethyl phosphite (0.2 ml) at room temperature for 30 min. The solvent was evaporated off and the residue was taken up in toluene (2 ml) and the mixture was evaporated (60 °C); this was repeated three times. The crude product was purified by chromatography, to yield compound (**17**) (25 mg, 76%) as an oil; $\nu_{max.}$ 3 500, 2 940, 1 740, 1 720, 1 480, 1 380, 1 180, 1 100, and 1 020 cm^{-1}; δ_H 0.91 (9 H, br s), 1.23 (3 H, s, 13-Me), 2.08 (3 H, s, 8-Me), 2.49 (2 H, s, 14-H_2), and 3.71 (OMe).

Alcohol (**7b**).—To a solution of the ester (**11b**) (140 mg, 0.40 mmol) in a 1:1 mixture of dioxane–water (10 ml) was added 10% aqueous sodium hydroxide (0.2 ml) and the mixture was heated under reflux for 45 min. The reaction mixture was cooled (0 °C) and brought to pH 3 with 10% hydrochloric acid, then extracted with ether (3 × 10 ml). The combined extract was washed with brine until neutral, dried, and evaporated to yield crude acid (**11a**) (120 mg).

Following the same procedure as in the preparation of compound (**16**), the acid (**11a**) (120 mg, 0.36 mmol) gave compound (**7b**) [75 mg, 53% from (**11b**)] as white *crystals*, m.p. 90—92 °C (from hexane); $[\alpha]_D$ +76.8° (*c* 0.74 in $CHCl_3$); $\nu_{max.}$ 3 300, 3 000—2 860, 1 745, 1 450, 1 380, 1 340, 1 210, 1 180, 1 100, 1 080, 1 050, and 980 cm^{-1}; δ_H 0.99 (3 H, s), 1.06 (3 H, s), 1.16 (3 H, s), 1.26 (3 H, s, 13-Me), 1.57 (3 H, s, 8-Me), 2.50 (2 H, br s, 14-H_2), 3.71 (OMe), and 4.08 (1 H, ddd, *J* 10.4, 8.8, and 6.4 Hz, 6-H); *m/z* 352 (M^+, 6%), 334 (7), 316 (8), 301 (10), 213 (58), 197 (22), 189 (32), 187 (100), 119 (71), 117 (68), and 69 (56) (Found: M^+, 352.2599. $C_{21}H_{36}O_4$ requires *M*, 352.2613).

Methyl 6-Epistrictanonate (**3b**).—Following the same procedure as for compound (**17**), ester (**7b**) (50 mg, 0.14 mmol) gave the title compound (**3b**) (45.0 mg, 87%) as an *oil*; $[\alpha]_D$ −184.3° (*c* 0.63 in $CHCl_3$); $\nu_{max.}$(neat) 3 000—2 850, 1 740, 1 720, 1 610, 1 450, 1 380, 1 350, 1 100, 1 040, 980, and 880 cm^{-1}; δ_H see Table 1; *m/z* 366 (M^+, 10%), 335 (4), 308 (19), 293 (9), 280 (25), 265 (9), 223 (32), 210 (15), 197 (39), 194 (16), 180 (10), 173 (9), 151 (28), 136 (37), 123 (25), 109 (36), 95 (34), 81 (25), 69 (45), 55 (25), 43 (100), and 41 (28) (Found: M^+, 366.2415. $C_{21}H_{34}O_5$ requires *M*, 366.2406).

Ketone (**12**).[12]—A stirred solution of epoxide (**9**) (50 mg, 0.14 mmol) in toluene (5 ml), under nitrogen was cooled (−20 °C) and treated with boron trifluoride–diethyl ether (0.1 ml) for 2 min. 10% Aqueous sodium hydrogen carbonate (3 ml) was then added and the mixture was extracted with ether (2 × 10 ml), and the combined extract was washed with brine until neutral, dried, and evaporated. The residue was pure ketone (**12**) (50 mg, 100%) as an oil; $[\alpha]_D$ +61.7° (*c* 0.7 in $CHCl_3$); $\nu_{max.}$(neat) 3 000—2 860, 1 750, 1 720, 1 650, 1 180, 1 030, and 895 cm^{-1}; δ_H 0.74 (3 H, s), 1.0 (3 H, s), 1.17 (3 H, s), 1.37 (3 H, s, 13-Me), 2.56 (2 H, s, 14-H_2), 2.76 (**1** H, s, 5-H), 2.81 (1 H, d, *J* 13.6 Hz, 7-H), 3.66 (4 H, s, OMe and br d, *J* 13.6 Hz, 7-H), 4.83 (2 H, dd, 17-H_2); *m/z* 348 (M^+, 43%), 333 (10), 275 (27), 234 (76), 197 (100), 196 (98), 164 (29), 163 (25), 151 (14), 150 (14), 123 (25), and 95 (36) (Found: M^+, 348.2280. Calc. for $C_{21}H_{32}O_4$: *M*, 348.2300).

Alcohol (**14b**).—To a solution of ketone (**12**) (260 mg, 0.75 mmol) in anhydrous ether (50 ml) was added a solution of freshly prepared zinc borohydride[24] in ether (17.5 ml, 1.4 mmol). The reaction mixture was kept at 18 °C for 30 h. After the reaction was complete (t.l.c.), the mixture was cooled (0 °C), water (10 ml) and acetic acid (1 ml) were added, and the mixture was stirred for 30 min. The ether layer was decanted, washed successively with 10% aqueous sodium hydrogen carbonate (2 × 20 ml) and brine until neutral, dried, and evaporated. The crude product (250 mg) was purified by chromatography to afford unchanged ketone (**12**) (33 mg, 0.09 mmol), the alcohol (**14b**) (153 mg, 59%), and its epimer (**11b**) (15 mg, 5%). Alcohol (**14b**) was an *oil*; $[\alpha]_D$ +1.5° (*c* 3.13 in $CHCl_3$); $\nu_{max.}$(neat) 3 520, 3 090, 2 980, 2 850, 1 740, 1 460, 1 445, 1 320, 1 260, 1 160, 1 050, 1 020, and 905 cm^{-1}; δ_H 1.00 (3 H, s), 1.08 (3 H, s), 1.19 (3 H, s), 1.28 (3 H, s, 13-Me), 2.52 (2 H, ABq, *J* 13.5 Hz, 14-H_2), 2.95 (2 H, br dd, 7-H_2), 3.63 (OMe), 4.31 (1 H, m, $w_{\frac{1}{2}}$ 13.0 Hz, 6-H), and 4.92 (2 H, br s, 17-H_2); *m/z* 350 (M^+, 11%), 332 (10), 317 (4), 301 (1), 277 (1), 258 (2), 225 (6), 218 (12), 198 (63), 197 (100), 165 (35), 123 (43), 109 (32), 95 (53), 91 (26), 84 (27), 81 (29), 69 (72), 59 (18), and 55 (52) (Found: M^+, 350.2433. $C_{21}H_{34}O_4$ requires *M*, 350.2457).

Alcohol (**7d**).—Following the same procedure as for compound (**7b**), the spirocompound (**14b**) (140 mg, 0.4 mmol) gave diol (**7d**) (105 mg, 75%) as an *oil*; $[\alpha]_D$ +3.37° (*c* 0.61 in $CHCl_3$); $\nu_{max.}$($CHCl_3$) 3 520, 2 990—2 860, 1 730, 1 610, 1 450, 1 390, 1 350, 1 140, and 1 100 cm^{-1}; δ_H 0.97 (3 H, s), 1.21 (3 H, s), 1.27 (3 H, s), 1.34 (3 H, s, 13-Me), 1.60 (3 H, br s, 8-Me), 2.51 (2 H, br s, 14-H_2), 3.71 (OMe), and 4.43 (1 H, br d, $w_{\frac{1}{2}}$ 9.5 Hz, 6-H); *m/z* 352 (M^+, 22%), 334 (19), 324 (8), 316 (8), 301 (32), 205 (35), 189 (85), 170 (82), 169 (87), 151 (25), 139 (20), 135 (22), 119 (32), 109 (41), 95 (42), 85 (25), 81 (31), 69 (62), 55 (43), and 43 (100) (Found: M^+, 352.2579. $C_{21}H_{36}O_4$ requires *M*, 352.2613).

Methyl Strictanonate (**2b**).[5,10]—Following the same procedure as for compound (**3b**), diol (**7c**) (30 mg, 0.09 mmol) gave the title compound (**2b**) (24.9 mg, 80%) as an oil; $[\alpha]_D$ +4.58° (*c* 2.5 in $CHCl_3$); $\nu_{max.}$(neat) 3 000—2 850, 1 740, 1 720, 1 450, 1 360, 1 240, 1 105, 1 030, and 880 cm^{-1}; δ_H see Table 1; *m/z* 366 (M^+, 2%), 351 (0.5), 335 (1.5), 308 (8), 293 (7), 280 (4), 265 (4), 250 (2), 235 (10), 223 (26), 197 (18), 194 (15), 179 (10), 176 (9), 173 (9), 161 (12), 155 (22), 151 (20), 136 (31), 109 (33), 95 (36), 81 (24), 69 (40), 55 (19), and 43 (100) (Found: M^+, 366.2405. Calc. for $C_{21}H_{34}O_5$: *M*, 366.2406).

Compound (**18**).—To a solution of compound (**2b**) (36.6 mg, 0.10 mmol) in a 1:1 mixture of dioxane–water (10 ml) was added 10% aqueous sodium hydroxide (0.1 ml) and the mixture was heated under reflux for 45 min. The solvent was evaporated off, the residue taken up into water (10 ml), and the solution was brought to pH 3 (10% hydrochloric acid), saturated with sodium chloride, then extracted with ether (3 × 10 ml). The combined extract was washed with brine until neutral, dried, and filtered. The filtrate was cooled (0 °C) and stirred with an excess of diazomethane in ether (30 min). The excess of

diazomethane was destroyed by addition of acetic acid and the solvent was evaporated off under reduced pressure. The crude residue was then purified by chromatography to afford pure diketo ester (**18**) (31.1 mg, 85%) as an *oil*; $\nu_{max.}$(neat) 3 400, 3 000—2 900, 1 750—1 720, 1 450, 1 380, 1 230, 1 220, 1 180, 1 150, 1 100, 1 060, and 1 030 cm^{-1}; δ_H see Table 1; *m/z* 366 (M^+, 1.4%), 348 (1), 333 (3), 317 (1.5), 309 (1), 301 (2.5), 291 (3), 275 (4), 259 (6), 250 (9), 241 (8), 235 (24), 223 (4), 217 (7.5), 193 (9), 189 (12.5), 177 (8), 159 (8), 150 (8), 123 (12.5), 117 (17.5), 109 (17), 95 (13), 85 (17), 69 (29), 55 (22), and 43 (100) (Found: M^+, 366.2391. $C_{21}H_{34}O_5$ requires *M*, 366.2403).

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