Absolute Stereochemistry of Soulattrolide and Its Analogues

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Received September 23, 1997

The absolute stereochemistry of a group of dipyranocoumarins, some of which are potent inhibitors of HIV-1 reverse transcriptase, was examined. Soulattrolide {2*H*,6*H*,10*H*-benzo[1,2-*b*:3,4-*b*′:5,6-*b*″]tripyran-2-one, 11,12-dihydro-12-hydroxy-6,6,10,11-tetramethyl-4-phenyl-, [10*S*-(10α,11*β*,12*β*)]-; CAS Registry No. 65025-62-9} and cordatolide B, two of these dipyranocoumarins, were converted to α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) derivatives and investigated by ^{1}H NMR spectroscopy. A correlation of ^{1}H NMR chemical shift differences with those predicted by Mosher's concept alone was inadequate to assign confidently the absolute stereochemistries, due to the fact that in both of these molecules too few protons are present on one side of the MTPA plane. However, energetically favored conformations obtained by molecular mechanics calculations provided satisfactory rationalizations for the observed anisotropic shifts in ^{1}H NMR data. The combined results of the two techniques allow us to assign the absolute configuration of both soulattrolide and cordatolide B as (10*S*,11*R*,12*S*). The absolute configurations of the other structurally related inhibitors, including inophyllums B, D, and P, costatolide, calanolides A, B, and C, and cordatolide A, are also assigned on the basis of chemical conversions and correlations of their chiroptical properties. Subtleties in the application of the Cahn−Ingold−Prelog rules to the designation of *R* or *S* configurations at some positions in these compounds make basically trivial errors particularly easy.

Introduction

The search for drugs for treating AIDS has led to the discovery of a group of dipyranocoumarins, isolated from several tropical plants of the genus *Calophyllum*. The compounds act as potent, nonnucleoside inhibitors of human immunodeficiency virus-1 reverse transcriptase (HIV-1 RT).[1−3] A characteristic set of heterocyclic rings fused to a phloroglucinol core constitutes the common feature of all these inhibitors. They differ from each other by the substituent group at C-4 and/or the chirality of the C-10, C-11, and C-12 stereogenic centers in the chromanol ring, as shown in Figure 1. Soulattrolide (**1**), which was characterized by Gunasekera et al.,[4] from a Sri Lankan plant, *C. soulattri*, and the stereoisomeric inophyllums A (**2**), B (**4**), D (**3**), and P (**5**) (from *C. inophyllum*)[1,2,5,6] bear a phenyl group at C-4. Another group of anti-HIV-1 dipyranocoumarins,[1] which bear a propyl substituent at C-4, includes costatolide (**6**) (isolated from *C. teysmannii*),[3a,7] calanolides A (**8**), B (**9**), and C (**7**) (from *C. lanigerum*),[1] and calanolide F (**10**) (from *C. teysmannii*).[8] The biological activity of a third group, with a methyl group at C-4, to which the cordatolides A (**12**) and B (**11**) (from *C. cordato-oblongum*)[9] belong, has not yet been reported.

Since a knowledge of the correct absolute configurations of these naturally occurring agents is essential for exploring structure−activity relationships and designing strategies for enantioselective syntheses, we undertook a stereochemical study of two of these dipyranocoumarins, soulattrolide (**2**) and cordatolide B (**11**), which were readily available to us. Although the relative stereochemistry of all the reported dipyranocoumarins has been established by ^{1}H NMR spectroscopy, absolute configurations had been reported only for four of them.[1,2,8] The absolute configurations of calanolides A (**8**), B (**9**), and F (**10**) and inophyllum A (**2**) had been determined and designated as (10*R*,11*R*,12*S*),[1] (10*R*,11*R*,12*R*),[1] (10*S*,11*R*,12*S*),[8] and (10*R*,11*S*,12*S*),[2] respectively. How-

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(10) Both these assignments were made using esters prepared by derivatizing the secondary OH group of the respective dipyranocoumarin. Although the assigned configurations are correct for the esters themselves, the parent secondary alcohols of these compounds should bear an opposite designation according to the Cahn−Ingold−Prelog priority rules. (See also note 15).

S0022-3263(97)01775-1 CCC: $15.00
Published on Web 01/30/1998

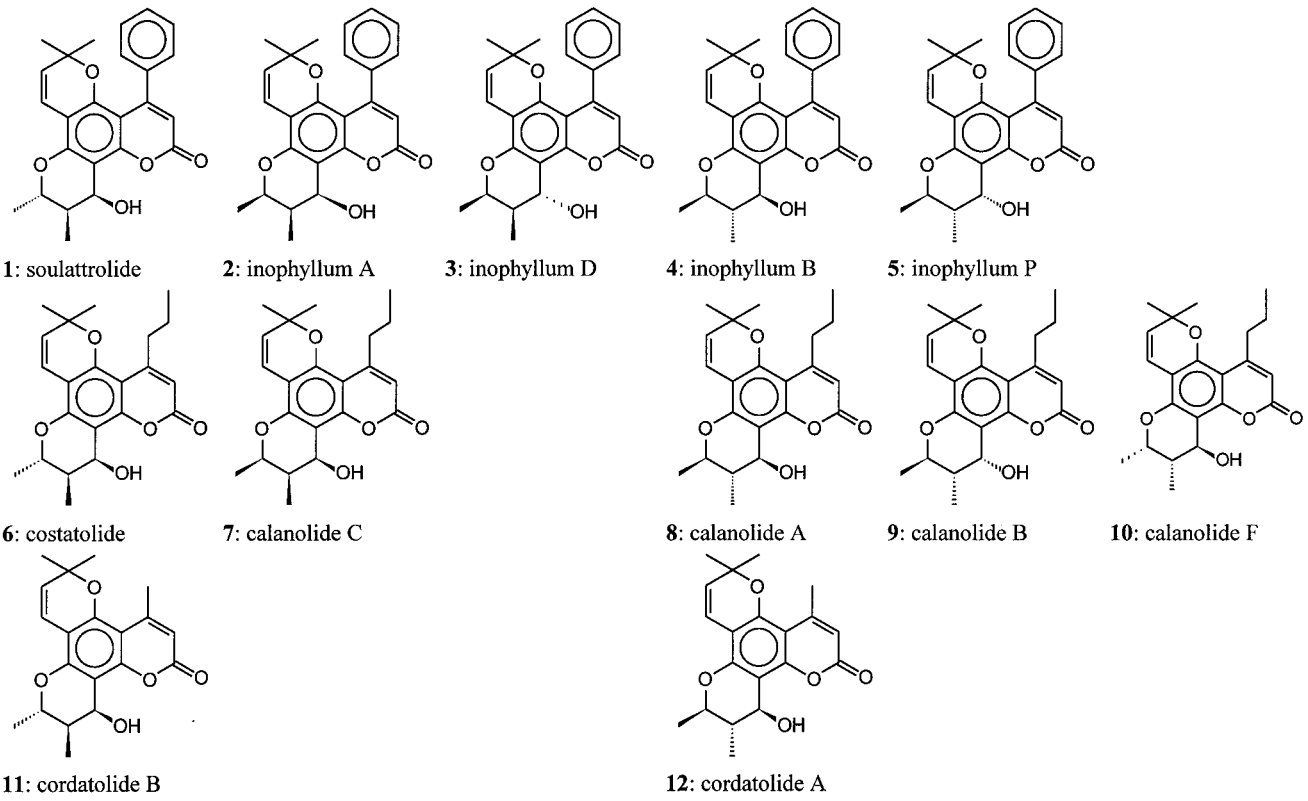

Figure 1. Structures of dipyranocoumarins.

Table 1. Absolute Configuration of Some Dipyranocoumarins

compd	name	$[\alpha]_D$	reported abs config	proposed abs config
1	soulattrolide	$[\alpha]^{27}_D$ −30.2°, *c* 0.4, $CHCl_3$[a]		(10*S*,11*R*,12*S*)
	[(−)-inophyllum P]	$[\alpha]^{27}_D$ −29.6°, $CHCl_3$[b]		
2	inophyllum A	$[\alpha]^{20}_D$ +43°, *c* 1.82, acetone[c]	(10*R*,11*S*,12*S*)[d]	(10*R*,11*R*,12*S*)
3	inophyllum D	$[\alpha]^{20}_D$ +35°, *c* 1.86, $CHCl_3$[c]		(10*R*,11*R*,12*R*)
4	inophyllum B	$[\alpha]^{20}_D$ +36°, *c* 0.72, acetone[c]		(10*R*,11*S*,12*S*)
5	inophyllum P	$[\alpha]_D$ +31.4°[d]		(10*R*,11*S*,12*R*)
	[(+)-soulattrolide]			
6	costatolide[e]	$[\alpha]^{25}_D$ −50.4°, *c* 1.55, acetone[f]		(10*S*,11*R*,12*S*)
	[(−)-calanolide B]	$[\alpha]^{20}_D$ −45.0°, *c* 1.0, acetone[g]		
7	calanolide C[h−j]	*k*		(10*R*,11*R*,12*S*)
8	(+)-calanolide A	$[\alpha]_D$ +60°, *c* 0.7, $CHCl_3$[h]	(10*R*,11*R*,12*S*)[h]	(10*R*,11*S*,12*S*)
		$[\alpha]^{20}_D$ +66°, *c* 0.5, $CHCl_3$[g]		
		$[\alpha]^{25}_D$ +68.8°, *c* 0.7, $CHCl_3$[l]		
8a	(−)-calanolide A	$[\alpha]^{20}_D$ −66°, *c* 0.5, $CHCl_3$[g]		(10*S*,11*R*,12*R*)
		$[\alpha]^{25}_D$ −75.6°, *c* 0.7, $CHCl_3$[l]		
9	(+)-calanolide B	$[\alpha]_D$ +10°, *c* 1.0, acetone[h,m]	(10*R*,11*R*,12*R*)[h]	(10*R*,11*S*,12*R*)
		$[\alpha]^{20}_D$ +44.0°, *c* 1.0, acetone[g]		
10	(−)-calanolide F	$[\alpha]_D$ −51.5°, *c* 0.35, $CHCl_3$[n]	(10*S*,11*R*,12*S*)[n]	(10*S*,11*S*,12*S*)
11	(−)-cordatolide B	$[\alpha]^{27}_D$ −26.2°, *c* 0.5, $CHCl_3$[a]		(10*S*,11*R*,12*S*)
		$[\alpha]_D$ −23.2°, $CHCl_3$[o]		
12	(+)-cordatolide A	$[\alpha]_D$ +54.8°, $CHCl_3$[o]		(10*R*,11*S*,12*S*)

[a] Rotation values from our measurements. Superscipts *b*, *c*, *d*, *f*, *g*, *h*, *i*, *j*, *l*, *m*, *n* and *o* correspond to refs 4, 6, 2, 7, 20, 1, 21, 18, 22, 23, 8, and 9, respectively. [d] The rotation value for inophyllum P reported in the discussion section of ref 2 is +31.4°. However, in the Experimental Section the value is given as +19.8°. Since inophyllum P (**5**) is the enantiomer of soulattrolide, the former value was considered to be the correct one. [e] (−)-Calanolide B is the preferred name for this compound (**6**),[23] since costatolide has been used later as the name of a completely unrelated compound.[24] [g] Synthetic compound.[20] [k] The value $[\alpha]_D$ +68° reported for calanolide C in ref 1 was later recognized as that for pseudocalanolide C.[19] [m] The optical rotation value reported[1] is low compared to that of its enantiomer, costatolide. Apparently the sample considered as natural (+)-calanolide B was a 11:9 scalemic mixture of (+) and (−) forms.[23]

ever, during our investigation we realized that the C-11 assignment given for **8**,[1] **9**,[1] **10**,[8] and **2**[2] is in fact erroneous[10] (see Table 1).

One of the most valuable and frequently used techniques for determining the absolute configuration of secondary alcohols, which depends on ^{19}F or ^{1}H NMR analysis of α-methoxy-α-(trifluoromethyl)phenylacetates, was developed by Mosher and co-workers.[11] The reliability of this method was increased considerably by Kakisawa and co-workers[12a,b] and others,[12c,d] by employing chemical shift differences of as many proton signals as possible rather than utilizing only two shift values as described in the conventional method. Both the original

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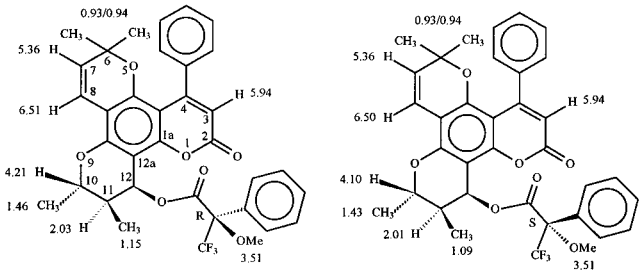

Figure 2. Some ^{1}H NMR data of (*R*)- and (*S*)-MTPA esters of soulattrolide.

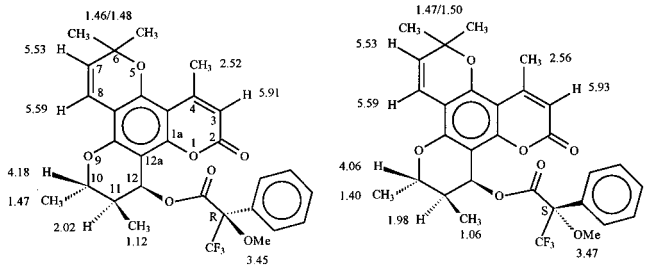

Figure 3. Some ^{1}H NMR data of (*R*)- and (*S*)-MTPA esters of cordatolide B.

and improved Mosher's method are based on an assumed, idealized conformation,[11] in which the carbinyl proton, ester carbonyl group, and trifluoromethyl group of an MTPA ester reside in the same plane. However, the flexibility of the MTPA moiety and the steric differences of substituents attached to the carbon atoms adjacent to the derivatized chiral center occasionally lead to unanticipated ^{1}H NMR shift variations.[12b] An alternative approach to improving the reliability of Mosher's method would be to obtain the preferred conformations by molecular modeling.[13]

In this work, we establish the absolute configurations of soulattrolide (**1**) and cordatolide B (**11**) by applying the improved Mosher method to conformations obtained from molecular mechanical calculations. We deduce the absolute configurations of other structurally related dipyranocoumarins by using their chiroptical properties and their known relationships with **1** and **11**.

Results and Discussion

^{1}H NMR Spectroscopy of Mosher Esters. The (*S*)- and (*R*)-MTPA esters were studied in $CDCl_3$, the preferred solvent for Mosher's method.[11] Since the derivatives proved to be rather unstable in $CDCl_3$, the acquisition of ^{1}H NMR data was completed within 5 min after the preparation of solutions. The ^{1}H NMR chemical shift differences observed in the spectra of (*S*)- and (*R*)-MTPA esters of soulattrolide (**1**) are illustrated in Figure 2. ^{1}H NMR data for both MTPA esters of **1** showed that the chemical shifts of the C-11 methyl group (δ 1.15) and C-11 proton (δ 2.03), and the C-10 methyl (δ 1.46) and C-10 proton (δ 4.21) in the (*R*)-MTPA ester of soulattrolide occur at lower field than the corresponding signals of the (*S*)-MTPA ester (δ: CH_3-C-11, 1.09; H-C-11, 2.01; CH_3-C-10, 1.43; H-C-10, 4.10). The chemical shift differences observed for these protons can be attributed to the differences in the anisotropic diamagnetic shielding effects resulting from two different orientations of the benzene ring of the (*R*)- and (*S*)-MTPA moieties. Unfortunately, no protons are attached to the C-12a, C-1a, O-1, C-2, and C-4 positions; even the solitary signal for the olefinic proton at C-3, which might have been anticipated to show some chemical shift difference for the two MTPA esters, appeared at the same shift value (δ 5.94). Although this situation was less than ideal, we tentatively assigned the absolute stereochemistry at C-12 as *S*, based on shift values for the CH_3-C-11, H-C-11, CH_3-C-10, and H-C-10 protons, which were smaller for the (*S*)-MTPA ester than those for the (*R*)-MTPA ester. Since the relative configuration of soulattrolide was already known,[4] it followed that the absolute configuration of **1** can be tentatively designated as (10*S*,11*R*,12*S*).

The ^{1}H NMR data obtained from the (*R*)- and (*S*)-MTPA esters of cordatolide B in $CDCl_3$ are summarized in Figure 3. Similar to the case of the soulattrolide MTPA esters, the chemical shifts of the C-11 methyl group (δ 1.12) and proton (δ 2.02) as well as the C-10 methyl (δ 1.47) and proton (δ 4.18) in the (*R*)-MTPA ester of soulattrolide occur at lower field than the corresponding signals of the (*S*)-MTPA ester (δ: CH_3-C-11, 1.06; H-C-11, 1.98; CH_3-C-10, 1.40; H-C-10, 4.06). However, the slight differences in the chemical shift values observed for the H-C-3, CH_3-C-4, and C-6 methyl signals of (*R*)- and (*S*)-MTPA esters were too small to be of diagnostic value. By using the improved empirical Mosher procedure, the absolute configuration at the C-12 position of cordatolide B (**11**) was tentatively identified as *S*, and the absolute configuration of cordatolide B (**11**) as (10*S*,11*R*,12*S*).

Nevertheless, the determination of absolute configuration based on chemical shift data for protons from only one side of the MTPA plane (due to the absence of protons at the C-12a, C-1a, O-1, C-2, and C-4 positions) is not an optimal way in which Mosher's protocol should be applied. Consequently, it appeared that obtaining a three-dimensional view of the interactions between the benzene ring of the MTPA moiety and various protons in the fused-ring system in the energetically most favored conformation, by computer modeling, would allow us to interpret the observed shift differences more reliably.

Molecular Mechanics Calculations. The energetically most favorable conformations for the (*S*)- and (*R*)-MTPA esters of soulattrolide (**1**) and cordatolide B (**11**) were obtained by a molecular mechanics procedure.[14] Although there is considerable conformational mobility, due to the presence of four rotatable bonds in the MTPA moiety, application of molecular mechanics and Monte Carlo procedures to (*R*)- and (*S*)-MTPA esters of soulattrolide and cordatolide B produced the lowest energy conformations depicted in Figures 4 and 5.

From the most favored conformations generated by the molecular dynamics calculations for both MTPA esters

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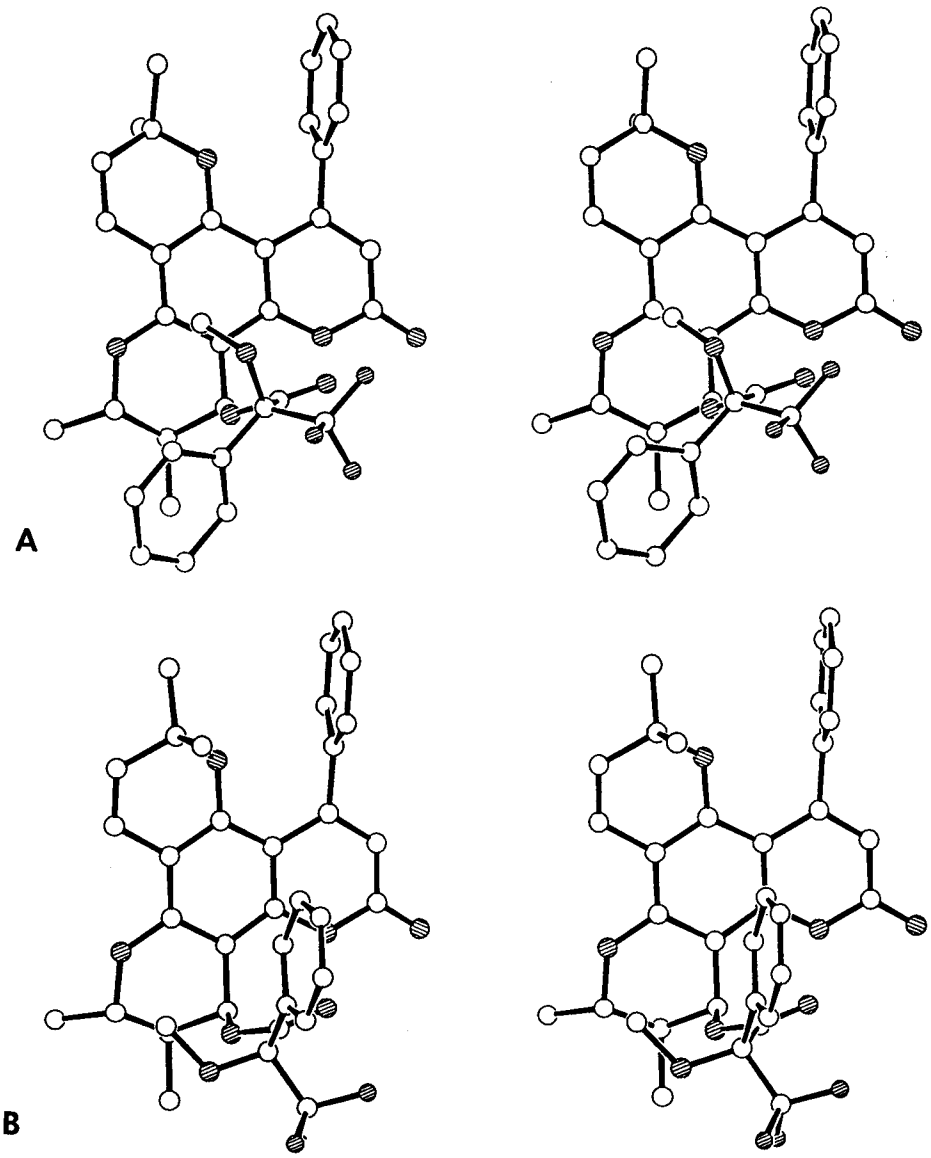

Figure 4. Stereoplots of lowest energy conformation of (*S*)-MTPA ester (A) and (*R*)-MTPA ester (B) of soulattrolide (hydrogen atoms not shown).

of soulattrolide (Figure 4), it is evident that the plane of the C-4 benzene ring attached to the fused-ring system is almost at right angles to the plane of the fused-ring system. Thus, the protons of the two methyl groups at the C-6 position are properly orientated relative to the benzene ring to experience the diamagnetic shielding effect of the aromatic ring current. In fact, the chemical shifts of the C-6 methyl protons in both soulattrolide esters occur considerably upfield (δ 0.93/0.94) of those observed for the cordatolide B esters (δ 1.46/1.48) which do not experience the influence of such a benzene ring. These results increased our confidence in finding satisfactory correlations between theoretically calculated conformations and the experimental NMR data.

Subsequently, we assessed the ^{1}H NMR differences between the (*S*)- and (*R*)-MTPA esters of soulattrolide. The favored conformations of the (*S*)- and (*R*)-MTPA derivatives, shown in Figure 4, reveal that in the (*S*)-MTPA ester of soulattrolide the benzene ring of the MTPA moiety is in close steric proximity to the C-10 and C-11 positions of the fused-ring system. On the other hand, in the (*R*)-MTPA ester of soulattrolide, the benzene ring of the MTPA moiety is oriented away from the C-10 and C-11 positions. These computer simulations are in accord with the observed experimental data which show that the chemical shifts for the protons at the C-10 and C-11 positions in the (*S*)-MTPA esters of soulattrolide appear upfield relative to those of the corresponding protons of the (*R*)-isomer (Figure 2). Similar chemical shift differences are observed in the spectra of the (*S*)- and (*R*)-MTPA esters of cordatolide B. As shown in Figure 5, in the lowest energy conformation, the benzene ring of the (*S*)-MTPA moiety of the cordatolide B derivative is tilted toward the fused-ring system in such a way that the protons at C-10 and C-11 are in the close proximity of the benzene ring. In contrast, the benzene ring in the (*R*)-MTPA moiety is completely turned away from the fused-ring system. These observations are in harmony with the relative chemical shifts obtained for the protons at the C-10 and C-11 positions in the spectra of the (*S*)- and (*R*)-MTPA esters of cordatolide B.

Absolute Configurations of Other Structurally Related Coumarins. Although the absolute configuration of inophyllum A (**2**) has been determined and

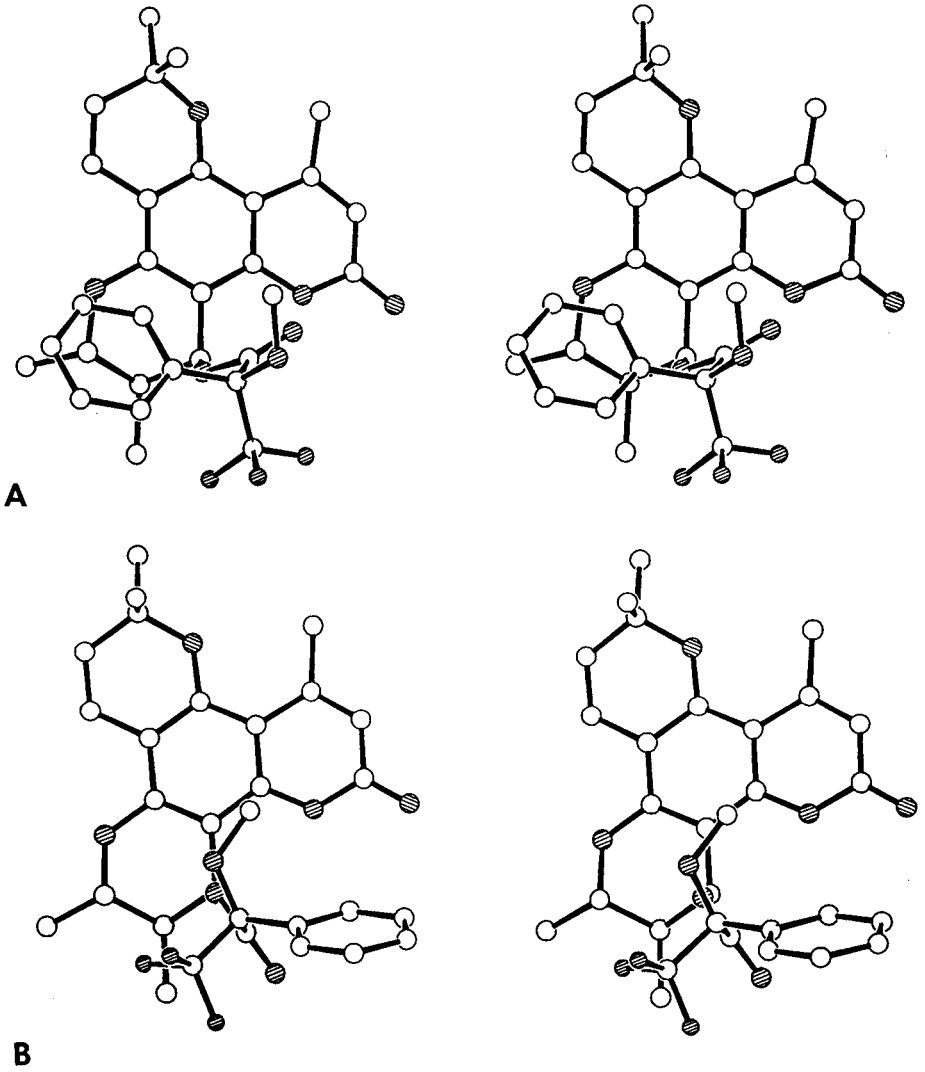

Figure 5. Stereoplots of lowest energy conformation of (*S*)-MTPA ester (A) and (*R*)-MTPA ester (B) of cordatolide B (hydrogen atoms not shown).

described previously as (10*R*,11*S*,12*S*) by an X-ray crystallographic study of its 4-bromobenzoate, the correct designation is actually (10*R*,11*R*,12*S*)[2] (a similar error is noted in the assignments of calanolides A,[1] B,[1] and F,[8] discussed in the next paragraph).[15] Since inophyllum D (**3**) is known to be the C-12 epimer of inophyllum A (**2**),[2] the absolute configuration of inophyllum D (**3**) must be (10*R*,11*R*,12*R*). It has been observed that chromic acid−pyridine oxidation of soulattrolide [(10*S*,11*R*,12*S*)-**1**] affords a ketone ($[\alpha]_D$ −45.9°)[4] that shows ^{1}H NMR data indistinguishable from those reported for natural inophyllum C, which in fact is identical to the oxidation product ($[\alpha]_D$ +54°)[6] of inophyllum B (**4**). However, the optical rotation of the oxidation product of soulattrolide (**1**) was opposite in sign to that of inophyllum C.[4] Therefore, we assigned the absolute configuration of the ketone inophyllum C as (10*R*,11*S*) and that of inophyllum B (**4**) as (10*R*,11*S*,12*S*). Finally, for inophyllum P (**5**) ($[\alpha]_D$ +31.4°), which is the enantiomer of soulattrolide ($[\alpha]_D$ −29.6°),[2,4] the absolute configuration must be (10*R*,-11*S*,12*R*).

The absolute configurations of calanolides A (**8**), B (**9**), and F (**10**) have been reported as (10*R*,11*R*,12*S*),[1] (10*R*,11*R*,12*R*),[1] and (10*S*,11*R*,12*S*).[8] A careful examination of the relevant data showed that the arguments used for these assignments are equivocal. The absolute configuration assigned to C-12 of calanolides A and B appears to be correct as a result of the two compensating errors.[1] The two MTPA esters derived from (*R*)-MTPA and (*S*)-MTPA chlorides have been named mistakenly[15] as the corresponding (*R*)- and (*S*)-MTPA esters, and the sign of the $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$) was reversed. Although the authors have made the two corrections subsequently in a corrigendum,[16] the assignment of the *R* configuration to C-11 of calanolides A (**8**) and B (**9**) is still incorrect. The *R* configuration at C-11 of the two MTPA derivatives from the alcohols, **8** and **9**, reverses to the *S* configuration after the MTPA moiety is replaced by a hydrogen atom, as a consequence of the change of

(15) It is important to note that an α-methoxy-α-(trifluoromethyl)-phenylacetate derivative (MTPA ester) of an alcohol such as 2-butanol bears the same stereochemical designation (*R* or *S*) as the alcohol itself. However, with certain structures of even slightly greater complexity, such as 1-methoxy-1-butanol, the ester of the *R* alcohol becomes an *S* ester entirely as a consequence of the Cahn−Ingold−Prelog priority rules.

(16) Kashman, Y.; Gustafson, K. R.; Fuller, R. W.; Cardellina, J. H., II; McMahon, J. B.; Currens, M. J.; Buckheit, R. W., Jr.; Hughes, S.; Cragg, G. M.; Boyd, M. R. *J. Med. Chem.* **1993**, *36*, 1110.

priorities according to the rules used for the determination of *R*/*S* configurations.[15] The correct absolute configurations of calanolides A (**8**) and B (**9**) should be (10*R*,11*S*,12*S*) and (10*R*,11*S*,12*R*), respectively. Calanolides C (**7**), the C-11 epimer of calanolides A,[1] is therefore (10*R*,11*R*,12*S*).[17−19] Since costatolide (**6**) has a relative configuration identical with that of calanolide B (**9**) but shows an optical rotation opposite to that of calanolide B (**9**), it must be the enantiomer of calanolide B (**9**) and its absolute configuration must be (10*S*,11*R*,12*S*) (Table 1).

The absolute configuration of cordatolide B (**11**), established as (10*S*,11*R*,12*S*) as described above, has the same relative and absolute stereochemical pattern in its chromanol ring as **1** and **6** (note: the structure illustrated for cordatolide B in refs 8 and 9 represents the enantiomer of cordatolide B). This stereochemical relationship between the three chiral centers of soulattrolide (**1**), costatolide [**6**, which in fact is the enantiomer of calanolide B], and cordatolide B (**11**) was also supported by their optical rotation values and signs [**1**, ($[\alpha]_D$ −29.6°); **6**, ($[\alpha]_D$ −19.9°); **11**, ($[\alpha]_D$ −23.2°)]. Form the data presented in Table 1, it is apparent that the sign of the optical rotation is determined essentially by the absolute configuration of the C-10 chiral center. In a previous report,[9] cordatolide A (**12**) was regarded as the C-12 epimer of cordatolide B (**11**) on the basis of the fact that the ^{1}H NMR data for the oxidation product of **11** were identical with those of the oxidation product of **12**. However, the positive rotation sign of **12** ($[\alpha]_D$ +54.8°) suggests that it bears a 10*R* configuration, similar to inophyllums and calanolides A, B, and C, all of which show a positive sign in optical rotations and have the 10*R* configurations. Therefore we propose the absolute configuration of cordatolide A to be (10*R*,11*S*,12*S*).

In summary, we have established the absolute configurations of soulattrolide (**1**), cordatolide B (**11**), and other related dipyranocoumarins (Table 1). These configurational assignments, which were hitherto either unknown or ambiguous, should facilitate enantioselective syntheses and structure−activity studies of this family of potent drug candidates. This combination of high-resolution NMR analyses with molecular mechanics calculations has potentially wider applications for determining the absolute configurations of other complex natural products well beyond the secondary alcohols and amines to which Mosher's method is currently applied.

Experimental Section

Materials. Soulattrolide ($[\alpha]^{27}_D$ −30.2°, *c* 0.4, $CHCl_3$) and cordatolide B ($[\alpha]^{27}_D$ −26.2°, *c* 0.5, $CHCl_3$) were obtained from Sri Lankan plants *C. soulattri* and *C. cordato-oblongum*, according to the procedures reported previously.[4,9] (*S*)-(+)- and (*R*)−(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chlorides were purchased from Aldrich Chemical Co.

Syntheses of (*S*)- and (*R*)-MTPA Esters. To a solution of soulattrolide (1.5 mg) in methylene chloride (50 mL) were injected dry pyridine (10 mL) and (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (5 mL). After the solution was kept at 0 °C for 48 h, the solvent was removed under vacuum and the residue was subjected to flash chromatography over silica gel (0.6 g, 60 μm, EM Science, Gibbstown, NJ). The column (25 cm × 0.3 cm) was eluted with ether/hexane (2:3), and fractions were monitored by TLC. Combination and concentration of the fractions containing product gave ca. 2.0 mg of the (*S*)-MTPA ester. Similarly, (*R*)-MTPA ester of soulattrolide was obtained using (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

In the same manner, the (*S*)- and (*R*)-MTPA esters of cordatolide B were obtained from the corresponding (*R*)-(+)- and (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.

Oxidation of Cordatolide B. To a solution of cordatolide B (2.0 mg) in CH_2Cl_2 were added 4 Å molecular sieves (two pellets), tetra-*n*-propylammonium perruthenate (0.2 mg), and *N*-methylmorpholine *N*-oxide (4 mg). The mixture was stirred for 1 h and subjected to column chromatography over silica gel (eluent: ether/hexane, 1:1) to yield 1.9 mg (95%) of the corresponding ketone ($[\alpha]_D$ −33.1°, *c* 0.19, $CDCl_3$).

NMR Spectroscopy. ^{1}H NMR spectra were obtained using a Varian Unity 500 MHz spectrometer. Chemical shifts are reported in ppm relative to the residual $CHCl_3$ peak in solvent $CDCl_3$ at 7.26 ppm.

Molecular Mechanics Calculations. The modeling of the structures of soulattrolide and cordatolide B were carried out using PCMODEL V. 4.0 software[14] which uses the MMX force field.[25] In the first stage of the calculation, possible configurations of the fused-ring part of the two alcohols were modeled. About 2000 conformations were generated for each compound, using the RANDOMIZE function available in PCMODEL.[14] All these conformations were optimized by minimizing their energies using a simulated annealing Monte Carlo procedure[26] and local energy minimization. For both compounds, only those conformations whose energies were within 10.0 kcal/mol of the lowest energies were considered further. In the second stage, the main parts of the MTPA moieties were appended to the energy-minimized fused-ring skeleton to create the structures of the (*R*)- and (*S*)-MTPA ester derivatives for soulattrolide and cordatolide B. To find low-energy conformations for each of the complete molecules, a Monte Carlo search was carried out followed by local energy minimizations. As a result, about 60 conformations were obtained for each of the (*R*)- and (*S*)-MTPA derivatives of soulattrolide and cordatolide B. Finally, the energy-minimized structures for each molecule were classified into families by cluster analysis[27] to obtain the typical lowest energy conformations of each molecule (Figures 4 and 5).

Acknowledgment. We thank Dr. S. P. Gunasekera, Prof. T. Kitahara, Prof. J. McMurry, and Prof. H. Mosher for helpful discussions and K. B. Herath for technical assistance. We gratefully acknowledge partial financial support of this research by NIH Grant GM53830.

JO9717752

(17) The data reported for calanolide C, which was originally thought to be present in *C. lanigerum*, was later shown to correspond to a different compound now called pseudocalanolide C (see refs 18 and 19).

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