Aromatic Resin Acid Ring Systems via Detosylation of Polyene Cyclization Derived Products

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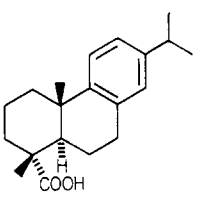
An efficient three-step strategy into resin acid type systems III and their cis isomers VI is presented. As illustrated by five examples, the method involves geranylation of sulfones **7a–c** and nerylation of **7a,b** to **8a–c** and **9a,b**, respectively. Subsequent FSO_3H–SO_2-promoted polyene cyclizations proceed stereospecifically and with asymmetric induction to produce epimeric diastereomers **10a–c/11a–c** and **12a,b/13a,b** in 60:40 and 70:30 ratios. Each epimeric set undergoes Dibal-H-mediated detosylation to provide diastereomeric compounds **15–19** in high yields.

Recent work from these laboratories has described clean and high-yield entries into some 4,5,6,7-tetrahydrobenzo[*b*]thiophenes, providing, e.g., systems exemplified by **3**, featuring a FSO_3H–SO_2-promoted cyclization of **1** and detosylation of the resulting **2** on treatment with diisobutylaluminum hydride (Dibal-H; Scheme I).[1] The strategy augments the amply documented synthetic power of the sulfone group[2] by showing the tosyl fragment to be inert toward the superacid cyclization conditions while displaying sufficient nucleofugicity to be displacable by Dibal-H-delivered hydride ion.[3] The tactic appeared to offer sufficient perspectives to merit further investigation. We therefore focused attention on some terminally prenylated homologues of **1**, denoted as I and IV and featuring opposite configurations about the olefinic bond. The present paper describes five specific examples thereof; their subsequent polyenic cyclizations to epimeric mixtures II and V, respectively and their ultimate detosylations to III and IV are presented (Scheme II). The motivation underlying these efforts stemmed from the recognition that ring system III agrees in framework, substitution pattern, and mode of ring junction with those of dehydroabietic and podocarpic acids **4** and **5**. Numerous routes thereto have



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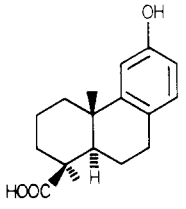

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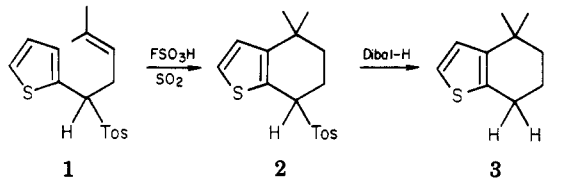
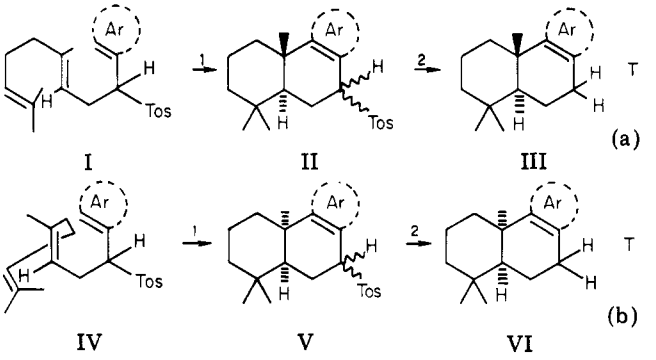
by now been elaborated,[4] but construction by way of biomimetically modeled polyenic cyclization schemes[5] has as yet received scant attention.[6] The advantages thereof would stem from their directness of purpose and, more important yet, the control of the cyclizations' stereochemical outcome. Assuming these to take place via synchronous pathways, Stork–Eschenmoser postulates[7] would predict polycyclizations of I to produce exclusively

Scheme I



1 **2** **3**

Scheme II[a]



I II III

IV V VI

[a] 1, FSO_3H-SO_2; 2, Dibal-H.

Table I. *E* and *Z* Cyclization Precursors

compd	yield,[a] %	mp, °C (recryst solvent)[b]
8a	53	62-63 (pentane)
8b	51	49-50 (pentane-diisopropyl ether)
8c	74	69-70 (diisopropyl ether)
9a	33	46-47 (pentane)
9b	42	48-49 (pentane)

[a] Based on the amount obtained with a melting point <5 °C below that of the analytical sample. [b] Satisfactory elemental analyses (C and H, ±0.3%) were found (supplementary material).

trans-fused II, with opposite geometry, i.e., V being expected on cyclizing IV. In addition, we were interested in examining the extent by which the steric demands of the tosyl fragment would bring about asymmetric induction in favor of β-tosylated tricyclic derivatives. Related asymmetric inductions had been achieved in steroid synthesis on cyclizing, for instance, suitably alkylated alicyclics to 6-α-methylestrone intermediates[8] and also their thiophene A-ring counterparts.[9] These results were rationalized in terms of cyclizations attaining early, prod-

(1) Janssen, C. G. M.; van Lier, P. M.; Schipper, P.; Simons, L. H. J. G.; Godefroi, E. F. *J. Org. Chem.* **1980**, *45*, 3159.
(2) For current reviews see: (a) Magnus, P. D. *Tetrahedron* **1977**, *33*, 2019. (b) Durst, T. In "Comprehensive Organic Chemistry"; Pergamon Press: Oxford 1979; Vol. 3.
(3) In the sulfones examined by us, the outcome of Dibal-H treatment differs from those of the literature: Gardner, J. N.; Kaiser, S.; Krubinev, A.; Lucas H. *Can. J. Chem.* **1973**, *51*, 1419.
(4) See ref 3 in: Huffman, J. W.; Harris, P. G. *J. Org. Chem.* **1977**, *42*, 2357.
(5) Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51.
(6) For a statement of intent hereto see: Macdonald, T. L.; Amirthalingam Narayanan, B.; O'Dell, D. E. *J. Org. Chem.* **1981**, *46*, 1504.
(7) See ref 3 and 4 in ref 5 of this paper.
(8) Groen, M. B.; Zeelen, F. J. *J. Org. Chem.* **1978**, *43*, 196.
(9) Macco, A. A.; de Brouwer, R. J.; Buck, H. M. *J. Org. Chem.* **1977**, *42*, 3196.

0022-3263/82/1947-3274$01.25/0

Table II. Methyl Chemical Shifts of Cyclized Materials[a]

entry (type)	compd	δ C-10 β-Me	δ C-4 α-Me	δ C-4 β-Me	Δδ C-10 β-Me	Δδ C-4 α-Me	Δδ C-4 β-Me
A (B/C-trans detosylated derivs)	15	1.30	0.93	0.93			
	16	1.15	0.91	0.87			
	17[b]	1.21	0.90	0.96			
	20[14]	1.18-1.22	0.94	0.94			
B (B/C-trans β-tosylated derivs)	10a	0.94	0.87	0.60	−0.21	−0.04	−0.27
	10b	0.88	0.82	0.62	−0.42	−0.11	−0.31
	10c	0.90	0.81	0.69	−0.31	−0.09	−0.27
C (B/C-trans α-tosylated derivs)	11a	1.02	0.90	0.79	−0.13	−0.01	−0.08
	11b	1.13	1.04	0.90	−0.17	0.11	−0.03
	11c	1.15	1.01	0.85	−0.06	0.11	−0.11
D (B/C-cis detosylated derivs)	18	1.17	0.63	0.99			
	19	1.27	0.67	1.00			
	21[14]	1.15	0.32	0.90			
E (B/C-cis α-toxylated derivs)	12a	0.90	0.40	0.62	−0.27	−0.23	−0.37
	12b	0.92	0.44	0.64	−0.35	−0.23	−0.36
F (B/C-cis β-tosylated derivs)	13a	1.36	0.84	1.17	0.19	0.25	0.14
	13b	1.45	0.83	1.11	0.28	0.16	0.11

[a] Data have been compiled according to chemical types. [b] This compound solidified and had a melting point of 70-71 °C.

Table III. Cyclized Sulfones

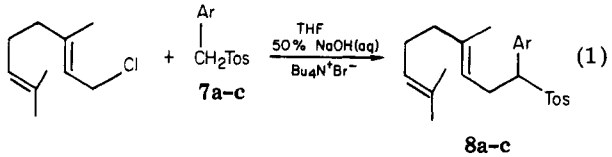
compd mixture	yield,[a] %	mp, °C	yield,[b] % (isolated compd)	mp, °C
10a/11a	62	133-151	16 (10a)	165-166
10c/11c	66	108-124	12 (10c)	138-139
			4 (11c)	129-131
12a/13a	80	126-135	24 (13a)	149-150
12b/13b	78	116-129	20 (13b)	140-141

[a] Crude mixture of α and β isomers. [b] Yield of actually isolated material having the reported melting point.

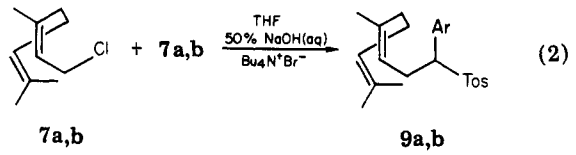
uctlike transition states, thereby shunning energetically unfavorable geometries involving counterproductive 1,3-interactions.

Results and Discussion

Synthesis of Starting Materials. Compounds **8a–c** and **9a,b** were prepared conveniently and in fair yields via phase-transfer alkylations of sulfones **7a–c** with geranyl[10] chloride and of **7a,b** with neryl chloride (eq 1 and 2). TLC



7a–c 8a–c (1)

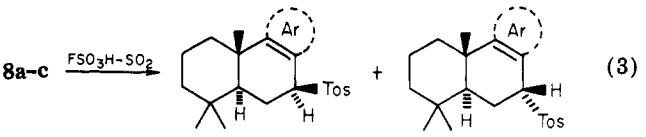


7a,b 9a,b (2)

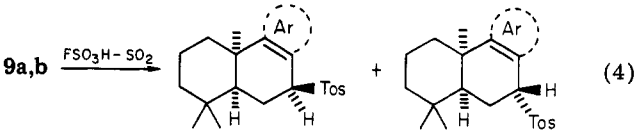
a, Ar = 2-thienyl; b, Ar = 3-thienyl; c, Ar = 3,5-dimethoxyphenyl

examination showed the crude product mixture to consist of unreacted sulfones and mono- and dialkylated products in addition to tarry contaminants. The required compounds were chromatographically isolated; their data are compiled in Table I.

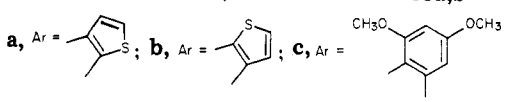
Cyclization Experiments. Ring closure conditions were based on those elaborated earlier[1] and involved dissolving the substrates **8a–c** and **9a,b** in 2 parts of liquid SO_2 containing catalytic or equivalent amounts of freshly distilled FSO_3H. Crude product mixtures were isolated after 15 min at −78 °C and were freed of polymeric byproducts by means of short column filtration. The resulting syrups were then examined via NMR (eq 3 and 4).



10a–c 11a–c (3)



12a,b 13a,b (4)



Geranyl and neryl systems **8a** and **9a,b** each furnished 60–80% of totally cyclized materials consisting of epimeric sets of α- and β-tosylated products. Estimation of component ratios and gross structural assignments were based on NMR inspection of the C-4 and the C-10 methyl shifts (Table II). For material arising from **8a** a 60:40 product distribution was noted; neryl systems **9a,b** produced more pronounced product spreads of 70:30. HPLC failed to bring about practically useful isomer separation, but, fortuitously, all product syrups eventually solidified. The crude solids obtained on cyclizing **8a** and which had melting points in the range 133–151 °C ultimately surrendered the least soluble and most abundant component (mp 165–166 °C) via repeated trituration (10% acetone–hexane). A similar procedure provided the pure major constituents of the crude solidified mixtures having originated from **9a,b**. Reasoning by analogy with the amply documented precedents of bulky substituents adopting the least encumbered configurations during polyenic cyclizations[5] (i.e., the phenomenon of chiral induction), we tentatively assigned β configurations **10a**, **12a**, and **12b** to the major isomers having arisen on cyclization of **8a** and **9a,b**

(10) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

since in these systems the tosyl fragments are clearly least encumbered by 1,3-interactions with the proximal C-9 proton; the minor components were therefore characterized as α epimers **11a**, **13a**, and **13b**. Definitive configurational assignments and also the unequivocal establishment of the mode of B/C ringfusion rested on spectral examination of subsequently detosylated materials and will be discussed in the section on Detosylation Experiments.

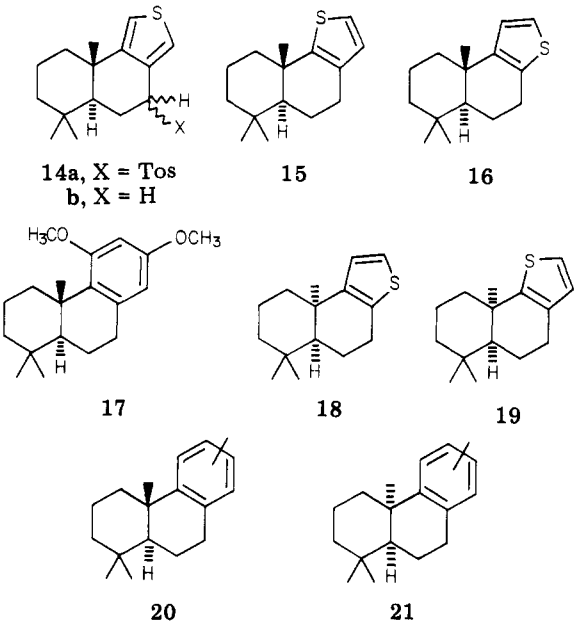
The data do not preclude the possibility of epimeric interconversions having occurred during the reactions' workup, thus disturbing initially produced product ratios. This was ruled out by ascertaining that pure **10a**, for instance, could be recovered unchanged from conditions simulating the isolation procedure (stirring for 18 h in ether–concentrated NH_4OH).

The (3-thienyl)geranyl system **8b** produced a considerably more complex mixture upon cyclization. NMR data again suggested the presence of a 60:40 mixture of epimers **10b/11b**, but ensuing detosylation (vide infra) produced two distinctly different compounds rather than the one expected on detosylating an epimeric pair. ^{13}C NMR inspection of the aromatic carbons confirmed the presence of detosylated **15** but showed it to contain ca. 30% of isomeric **14b**. The latter must have arisen out of an uncommon cyclization of **8b** onto the 4-thiophene position to produce **14a** and, on detosylation, **14b**. A comparable low-temperature cyclization anomaly had been demonstrated earlier and was attributed to the 3-thienyl substituent retarding attainment of suitable conformations necessary for producing 2,3-annelated thiophenes only.[11] It is interesting, though, to note that no detectable 3,4-thiophene annelation was observed on cyclizing neryl analogue **9b**.[12] The crude solidified mixture resulting from cyclization of **8b** ultimately provided homogeneous material on prolonged trituration with acetone–hexane and was spectrally identified as **10b**.

The dimethoxyphenyl precursor **8c** gave, after 15 min in SO_2–FSO_3H, an oily 60:40 mixture of ring-closed epimers from which was isolated 12% of the major β isomer **10c**, mp 138–139 °C. The mother liquors ultimately deposited a small amount of the α isomer (mp 129–131 °C), thereby providing the only instance of actual isolation of both of the produced epimers. Physical data relating to all cyclized materials are gathered in Table III.

Our cyclization data merit additional comment. Polyene cyclization represents intramolecular electrophilic addition across a double bond, with the olefin, electrophile, and nucleophile all being located within the molecule and suitably positionable with respect to each other. The process, initiated by acid-induced activation of the electrophile (i.e., generation of the initiator), hence proceeds concertedly with the olefin bonding to the initiator while the nucleophile, as terminator, attaches itself to the incipient cation. Whereas olefins have found extensive use as reaction terminators, efforts to have them function as electrophilic initiators by way of terminal olefinic protonation have been disappointing.[13] This has been ascribed to indiscriminate protonation of the polyene triggering off undesirable side reactions. The consistently high yields attained in our SO_2-conducted olefin-initiated polycyclizations are at variance with the literature failures which may well be attributable to the SO_2 solvating and stabilizing the incipient cations.

Chart I

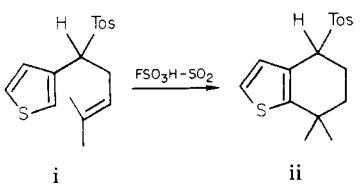


Detosylation Experiments. Pure β isomers **10a,c** and **12a,b** were treated with Dibal-H in toluene for 5 min at 50 °C to provide detosylated systems **16–19** (Chart I). Exactly identical, homogeneous materials were arrived at on detosylating the binary mixtures **10a/11a**, **10c/11c**, **12a/13a**, and **12b/13b**, thus providing unequivocal proof of the compounds of each mixture differing in the configurational mode of tosyl attachment only. Spectral examination provided conclusive evidence for the nature of the B/C ring fusion of all systems in question, since closely related (trans) **20** and (cis) **21** had previously been described by Wenkert et al.[14] The close similarity of methyl shifts of **16** and **17** to those reported for **20** suggest that **16** and **17**, and therefore **10a,c** and **11a,c**, constitute B/C trans-annelated systems. Likewise, the resemblance of methyl shifts of **18** and **19** to those of **21** implicate **18** and **19**, together with their predecessors **12a,b** and **13a,b**, as the B/C cis-fused counterparts. Specific data are gathered in Table II, entries A and D. The products **14b/15**, having arisen out of the detosylation of the total cyclization harvest of **8b**, were also spectrally similar to **20** and were therefore designated as B/C trans-fused ring systems.

The spectral data also served to substantiate the previously tentative tosyl configurational assignments. Inspection of molecular models of trans-fused systems shows the C-4 and C-10 methyl groups to be in the shielding cone of the tosyl substituent. They are closer to the tosyl group in the β configuration; hence the detosylation of all systems to **16–17** ought to bring about a greater upfield shift in methyl signals for β isomers than for α analogues. Similarly, cis-fused systems show the C-4 and C-10 methyl

(11) Macco, A. A.; de Brouwer, R. J.; Nossin, P. M. M.; Godefroi, E. F.; Buck, H. M. *J. Org. Chem.* **1978**, *43*, 1591.

(12) The previously reported cycloalkylation of i also appeared by several criteria to have proceeded unidirectionally to ii:



Crude material, obtained in 92% yield, had a melting point agreeing with that of the analytical sample and showed no NMR evidence of 3,4 ring closure having occurred.

(13) See ref 1 in ref 5 of this paper.

(14) Wenkert, E.; Afonso, A.; Beak, P.; Carney, R. W. J.; Jeffs, P. W.; McChesney, J. D. *J. Org. Chem.* **1965**, *30*, 713.

Table IV. ^{1}H NMR Data

compd	^{1}H NMR ($CDCl_3$), δ
8b	1.52, 1.56, 1.60 (3 s, 9, 3 CH_3), 1.77–2.10 (m, 4, CH_2CH_2), 2.38 (s, 3, TosCH$_3$), 2.47–3.39 (m, 2, TosCCH_2), 3.95–4.34 (dd, 1, CHTos). 4.63–5.13 (m, 2, olefinic H), 6.77–7.53 (m, 7, Ar H)
8c	1.52, 1.57, 1.58 (3 s, 9, 3 CH_3), 1.76–2.11 (m, 4, CH_2CH_2), 2.36 (s, 3, TosCH$_3$), 2.52–3.20 (m, 2, TosCCH_2), 3.60 (s, 6, 2 OCH_3), 3.73–4.06 (dd, 1, CHTos), 4.59–5.06 (m, 2, olefinic H), 6.03–6.34 (m, 3, Ar H), 6.93–7.54 (AB, 4, sulfone Ar H)
9a	1.53 (s, 6, =C(CH_3)$_2$), 1.64 (s, 3, =CCH_3), 1.84–2.13 (m, 4, CH_2CH_2), 2.13–3.26 (m, 2, TosCCH_2), 2.37 (s, 3, TosCH$_3$), 3.87–4.23 (dd, 1, CHTos), 4.64–5.20 (m, 2, olefinic H), 6.50–7.48 (m, 3, Ar H)
9b	1.59, 1.60, 1.69 (3 s, 9, 3 CH_3), 1.81–2.14 (m, 4, CH_2CH_2), 2.38 (s, 3, TosCH$_3$), 2.53–3.41 (m, 2, TosCCH_2), 3.90–4.28 (dd, 1, CHTos), 4.60–5.23 (m, 2, olefinic H), 6.76–7.54 (m, 7, Ar H)
10b	0.48–2.63 (m, 9, 4 CH_2 and CH), 0.62, 0.82, 0.88 (3 s, 9, 3 CH_3), 2.36 (s, 3, TosCH$_3$), 4.14–4.69 (m, 1, CHTos), 6.87–7.70 (m, 6, Ar H)
10c	0.49–3.25 (m, 9, 4 CH_2 and CH), 0.69, 0.81, 0.90 (3 s, 9, 3 CH_3), 2.34 (s, 3, TosCH$_3$), 3.69 (d, 6, 2 OCH_3), 4.32–4.81 (m, 1, CHTos), 6.21–7.41 (m, 6, Ar H)
11c	0.77–3.23 (m, 9, 4 CH_2 and CH), 0.85, 1.01, 1.15 (3 s, 9, 3 CH_3), 2.40 (s, 3, TosCH$_3$), 3.69 (d, 6, 2 OCH_3), 4.19–4.50 (m, 1, CHTos), 6.31–6.62 (AB, 2, Ar H), 7.06–7.74 (AB, 4, sulfone Ar H)
13a	0.56–2.64 (m, 9, 4 CH_2 and CH), 0.84, 1.17, 1.36 (3 s, 9, 3 CH_3), 2.36 (s, 3, TosCH$_3$), 4.14–4.59 (m, 1, CHTos), 6.56–7.89 (m, 6, Ar H)
13b	0.66–2.53 (m, 9, 4 CH_2 and CH), 0.83, 1.11, 1.45 (3 s, 9, 3 CH_3), 2.33 (s, 3, TosCH$_3$), 4.01–4.48 (m, 1, CHTos), 6.79–7.67 (m, 6, Ar H)
17	0.90, 0.96, 1.21 (3 s, 9, 3 CH_3), 0.77–1.98 (m, 8, 4 CH_2), 2.54–3.23 (m, 3, ArCH_2 and CH), 5.76–6.20 (m, 2, Ar H)
18	0.63, 0.99, 1.17 (3 s, 9, 3 CH_3), 0.77–2.54 (m, 9, 4 CH_2 and CH), 2.63–3.06 (m, 2, ThCH_2), 6.68–7.08 (AB, 2, Ar H)
19	0.67, 1.00, 1.27 (3 s, 9, 3 CH_3), 1.00–2.45 (m, 9, 4 CH_2 and CH), 2.45–2.89 (m, 2, ThCH_2), 6.41–6.99 (AB, 2, Ar H)

groups in the β configuration to lie in the deshielding cone of the tosyl group; in the α forms they are situated in the shielding cone. Hence detosylation of all systems to **18** and **19** should bring about a downfield shift for the β isomers and an upfield shift for the α isomers. This is borne out by experimental observations. As shown in Table II (entries B, C, E, F), all observed $\Delta\delta$'s are greater for β isomers **10a,c** than for α epimers **11a,c**, whereas the signs of **12a,b** are opposite to those of **13a,b**, thus firmly establishing the nature of the tosyl configuration at the C-6 position of all cyclic intermediates.

Conclusions

For practical purposes, the outlined route constitutes the method of choice for preparing aromatic resin acid derived systems III. The overall concept centers on the concerted and totally stereospecific polyene cyclization of I to II. Type I, already featuring the correct array of carbon atoms with fixed geometry, is easily assembled from cheap and plentiful components via open-vessel, aqueous, phase-transfer techniques. The approach has the tosyl moiety functioning as an auxiliary fragment. Its carbanion-stabilizing properties allow construction of I; it survives cyclization conditions to II and may ultimately be removed on treatment with Dibal-H. We are continuing investigations to determine the scope and limitations of this strategy.

Experimental Section

General Methods. The authors thank Messrs. P. van den Bosch and H. Eding for microanalytical data. ^{1}H NMR spectra were obtained on a Varian EM 360 spectrometer. Melting points (recorded on a Fisher-Johns block) are uncorrected. Chromatography was carried out over a 10-fold weight of silica gel.

(3,5-Dimethoxyphenyl)(*p*-toluenesulfonyl)methane (7c) was obtained (88%) from the chloride as described for **7a,b**.[1] A sample was purified from 2-propanol: mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3, TosCH$_3$), 3.61 (s, 6, 2 OCH_3), 4.15 (s, 2, CH_2), 5.96–6.45 (m, 3, Ar H), 6.95–7.64 (AB, 4, sulfone Ar H).

Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92. Found: C, 62.65; H, 6.00.

1-Chloro-3,7-dimethyl-2(*Z*),6-octadiene was prepared according to the method described for the *E* isomer:[10] yield 76%; bp 48–50 °C (0.25 mm); ^{1}H NMR (CCl_4) δ 1.59, 1.65, and 1.77 (3 s, 9, 3 CH_3), 2.02 and 2.11 (2 s, 4, 2 CH_2), 3.89 (d, 2, CH_2Cl), 4.75–5.52 (m, 2, olefinic H).

The preparation of cyclization precursors **8a–c** and **9a,b** (Table I) is exemplified by the synthesis of **8a**.

***dl*-1-(2-Thienyl)-1-(*p*-toluenesulfonyl)-4,8-dimethyl-3-(*E*),7-nonadiene (8a).** A mixture of 12.6 g (0.05 mol) of **7a**,[1] 9.5 g (0.055 mol) of geranyl chloride,[10] 75 mL of 50% sodium hydroxide, 20 mL of THF, and 1.0 g of tetrabutylammonium bromide was thoroughly stirred for 18 h at room temperature. Water (500 mL) was then added. The organic layer was separated and diluted with ether. The ether phase was washed with brine until neutral, dried, and evaporated to leave 20.0 g of crude material. Chromatography (eluent hexane/10% acetone), evaporation, and trituration with low-boiling petroleum ether gave 10.3 g (53%) of solid material, mp 60 °C. Recrystallization from pentane furnished analytical material: mp 62–63 °C ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3, =CCH_3), 1.54 (s, 6, C=C(CH_3)$_2$), 1.60–2.06 (m, 4, CH_2CH_2), 2.38 (s, 3, TosCH$_3$), 2.38–3.43 (m, 2, TosCCH_2), 3.93–4.35 (dd, 1, CHTos), 4.57–5.12 (m, 2, olefinic H), 6.56–7.53 (m, 7, Ar H).

Anal. Calcd for: $C_{22}H_{28}O_2S_2$: C, 68.00; H, 7.26. Found: C, 68.20; H. 7.47.

The preparation procedure leading to **10a–c** and **11a–c** and to **12a,b** and **13a,b** (Table III) is given in detail for **10a**.

***dl*-4aβ,7,7-Trimethyl-9β-(*p*-toluenesulfonyl)-4,4a,5,6,7,7aα,8,9-octahydronaphtho[1,2-*b*]thiophene (10a).** To a solution of 5 g (0.014 mol) of **8a** in 10 mL of liquid sulfur dioxide at −78 °C was added 0.5 mL (0.008 mol) of freshly distilled fluorosulfuric acid. The mixture was stirred for 5 min and was then quenched by addition of NaOMe (from 0.5 g of Na) in a little methyl alcohol. The resulting solution was then poured into an ether–water mixture. The ether layer was washed with water (3×), with cold 5 N NH_4OH solution (3×), and then with water until neutral. Drying and evaporation left 3.8 g of crude material. Chromatography gave 3.1 g (62%) of an oil which solidified on prolonged standing. Trituration with hexane/10% acetone gave 1.9 g of solid material (38%), consisting of an α/β mixture of tosyl epimers **10a/11a**, mp 133–151 °C. Repeated trituration with hexane/10% acetone on ice provided 0.8 g (16%) of the pure β isomer: mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 0.60, 0.87, and 0.94 (3 s, 9, 3 CH_3), 0.90–2.45 (m, 9, 4 CH_2 and CH), 2.38 (s, 3, TosCH$_3$), 4.58 (dd, 1, CHTos), 6.57–7.89 (2 AB, 6, Ar H).

Anal. Calcd for: $C_{22}H_{28}O_2S_2$: C, 68.00; H, 7.26. Found: C, 67.80; H, 7.25.

Detosylation experiments leading to compounds **15–19** (Table IV) are typified by the hydrogenolysis of epimeric mixture **10a/11a**.

***dl*-4aβ,7,7-Trimethyl-4,4a,5,6,7,7aα,8,9-octahydronaphtho[1,2-*b*]thiophene (16).** To a stirred nitrogen-covered

solution of 0.39 g (0.001 mol) of **10a/11a** in 0.4 mL of dry toluene at 50 °C was added, in one portion, 0.21 g (0.0015 mol) of Dibal-H in 1 mL of toluene. Isobutene was evolved as the temperature rose to 80 °C. After 5 min the mixture was cooled, and to it were carefully added 0.1 mL of ethanol, 0.45 mL of water, and 0.225 mL of concentrated hydrochloric acid. The organic layer was decanted, and the residue was extracted with diethyl ether. The combined organic layers were washed with water, 5 N sodium hydroxide solution, and water until neutral, dried, and evaporated to leave 0.25 g of crude material. Filtration through silica with hexane gave 0.19 g of **16** (81%). The compound was pure: ^{1}H NMR, TLC, and HPLC pure: ^{1}H NMR ($CDCl_3$) δ 0.87, 0.91, and 1.15 (3 s, 9, 3 CH_3), 1.06–2.26 (m, 9, 4 CH_2 and CH), 2.61–3.00 (m, 2, $ThCH_2$), 6.56–7.02 (AB, 2, Ar H).

Registry No. **7a**, 20895-79-8; **7b**, 73838-25-2; **7c**, 82112-37-6; (±)-(*E*)-**8a**, 82112-38-7; (±)-(*E*)-**8b**, 82112-39-8; (±)-(*E*)-**8c**, 82112-40-1; (±)-(*Z*)-**9a**, 82112-41-2; (±)-(*Z*)-**9b**, 82112-42-3; (±)-**10a**, 82112-43-4; (±)-**10b**, 82112-44-5; (±)-**10c**, 82112-45-6; (±)-**11a**, 82166-43-6; (±)-**11b**, 82166-44-7; (±)-**11c**, 82112-46-7; (±)-**12a**, 82116-45-8; (±)-**12b**, 82166-46-9; (±)-**13a**, 82166-47-0; (±)-**13b**, 82166-48-1; **14a**, 82112-47-8; (±)-14b, 82112-48-9; (±)-**15**, 82112-49-0; (±)-**16**, 82112-50-3; (±)-**17**, 82112-51-4; (±)-**18**, 82112-52-5; (±)-**19**, 82112-53-6; 1-chloro-3,7-dimethyl-2(*Z*),6-octadiene, 20536-36-1; geranyl chloride, 5389-87-7.

Supplementary Material Available: Table of recrystallization solvents, formulas, and C and H elemental analyses for **8b,c**, **9a,b**, **10c**, **13a,b**, and **17** (1 page). Ordering information is given on any current masthead page.

Microbial Transformations of Natural Antitumor Agents. 21. Conversions of Aphidicolin

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Microbial transformations have been employed as a means of preparing analogues of the diterpene aphidicolin. Microbial transformation products were initially identified by thin-layer chromatography of fermentation extracts and then were prepared by larger scale incubations. Each microbial metabolite was subjected to structure elucidation employing carbon-13 and proton NMR, high-resolution mass spectrometry, and infrared analysis. Metabolites were identified as 3α-acetoxy-16,17,18-trihydroxyaphidicolane, 18-acetoxy-3α,16,17-trihydroxyaphidicolane, 3α,16,17-trihydroxyaphidicolan-18-oate, 16,17,18-trihydroxyaphidicolan-3-one, 3β,16,17,18-tetrahydroxyaphidicolane, and 3α,6β,16,17,18-pentahydroxyaphidicolane. The availability of the microbial metabolites enabled the near complete elucidation of the carbon-13 NMR spectrum of aphidicolin. Biological evaluations of these compounds were made by using in vivo and in vitro techniques. None of the metabolites were active in an in vivo antitumor test system, while all of the compounds inhibited the uptake of thymidine to P-388 leukemic cells in vitro.

Introduction

3α,16,17,18-Tetrahydroxyaphidicolane (aphidicolin, 1, Figure 1) is a novel diterpene produced by species of *Cephalosporium aphidicola*[1] and *Nigrosporum sphaerica*.[2] This compound possesses antiviral[1,3] and antitumor activities[4] while demonstrating a lack of mutagenic activity.[5] Aphidicolin is very specific in inhibiting DNA polymerase α.[6,7] These interesting biological properties have prompted the preparation of various derivatives of aphidicolin[8] as well as partial[9] and total synthetic efforts.[10,11]

The structural complexity of aphidicolin renders the preparation of unusual analogues a difficult task. Aphidicolin analogues would be of interest to exploit the known biological activities and to establish structure activity relationships for the unusual diterpene. Microbial transformations have been widely employed in the preparation of difficult-to-synthesize analogues of steroids and structurally complicated antitumor compounds.[12] This report describes the preparation of six analogues of aphidicolin using microbial transformation technology, the elucidation of most of the carbon-13 NMR spectrum of aphidicolin, and a description of the biological activities of the aphidicolin analogues.

Discussion

The outstanding successes realized in microbial transformations of steroids and of other terpenes[12] indicated that a similar approach with aphidicolin could provide interesting new analogues. A broad program of screening microorganisms for their abilities to achieve useful chemical transformations of aphidicolin was undertaken. Some 220 cultures were examined, and numerous of these pro-

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