Highly Stereoselective Total Syntheses of (+)-Pachydictyol A and (−)-Dictyolene, Novel Marine Diterpenes from Brown Seaweeds of the Family Dictyotaceae

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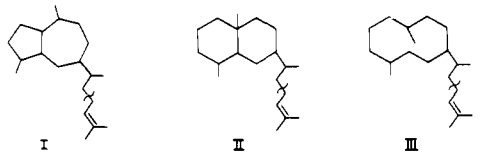
Abstract: (+)-Pachydictyol A (**1**) and (−)-dictyolene (**2**), unusual diterpene alcohols from Dictyotaceae, have been stereoselectively synthesized from (−)-α-santonin (**3**). In each of the syntheses, a reduction–olefin transposition (**5** → **8b**, **11a** → **16**) is used as the key step, introducing the required 5β-H and the C-3, C-4 double bond.

Introduction

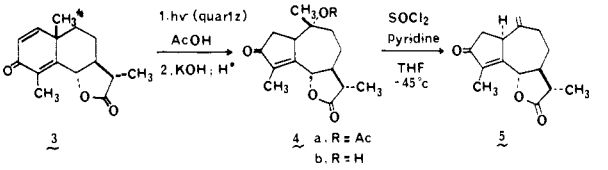
The brown seaweeds (*Phaeophyta*) of the family Dictyotaceae produce a variety of novel and potentially useful metabolites[1]. Of particular interest in this family are several species of the genus *Dictyota*. Extracts from these algae, which are found generally in shallow water and intertidal communities in subtropical and tropical areas[2], exhibit a remarkably broad range of biological properties, which include cytotoxic[3], antibacterial[4], antiviral[5], antitumor[6], and antifungal effects[6]. It is of undeniable interest to the synthetic organic chemist that these extracts as well as those from certain related genera have recently yielded a number of unique "prenylated sesquiterpenes", i.e., diterpenes that are formally composed of typical sesquiterpene skeletons to which an additional isoprene unit has been added. Examples have been found in the guaiane (I), eudesmane (II), and germacrane (III) skeletal classes.



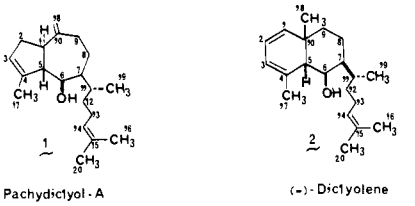
I II III

Pachydictyol A (**1**)[8,9], the first such prenylated sesquiterpene to be isolated and fully elucidated, is the structural prototype of a number of subsequently discovered guaiane-type diterpenes,

Scheme I



among which are pachydictyol A epoxide[2], dictyoxide[10], dictyols A, B, C, D, and E[8b,d,f,11], dictyol B acetate[8f], and dictyotadiol[8f]. Dictyolene (**2**) is probably the most prominent member of the relatively small group of prenylated eudesmanes known to date[12]. The germacrane skeleton, on the other hand, is incorporated in a somewhat larger number of diterpenes including dilophol[8c], dilopholone[13], epoxydilophone[13], acetoxydilopholone[13], and *epi*-acetoxydilopholone[13].



In this paper a full report is given of our work in this fascinating new area of marine natural products. Our efforts resulted in both a highly stereoselective total synthesis of natural pachydictyol A (**1**), constituting the first recorded synthesis of any of these novel diterpenes, and a completely stereoselective total synthesis of (−)-dictyolene (**2**)[14,15].

Results and Discussion

(+)-Pachydictyol A. (+)-Pachydictyol A (**1**) was first isolated from *Pachydictyon coriaceum* by Sims and co-workers[8a] in 1973 and was later found in the extracts from the related algae *Dictyota dichotoma*[8b] and *Dilophus ligulatus*[8c], all of the family Dictyo-

(1) For recent reviews on marine natural product chemistry, see: (a) Baker, J. T.; Murphy, V. "Compounds from Marine Organisms", Vol. 1; CRC Press: Cleveland, 1976. (b) Faulkner, D. J., Fenical, W. H., Eds. "Marine Natural Products Chemistry"; Plenum Press: New York, 1977. (c) Faulkner, D. J. *Tetrahedron* **1977**, *33*, 1421. (d) Scheuer, P. J., Ed. "Marine Natural Products, Chemical and Biological Perspectives"; Academic Press: New York, 1978.

(2) Robertson, K. J.; Fenical, W. *Phytochemistry* **1977**, *16*, 1071.

(3) Hashimoto, Y.; Fusetani, N.; Nozawa, K. *Proc. Int. Seaweed Symp. 7th* **1971**, 569.

(4) Berti, T.; Fassina, G.; Pignatti, S. *G. Bot. Ital.* **1963**, *70*, 609. Burkholder, P. R.; Burkholder, L. M.; Almodovar, L. R. *Bot. Mar.* **1968**, 11, 149. Hornsey, I. S.; Hide, D. *Br. Phycol. J.* **1974**, *9*, 353.

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(6) Kashiwagi, M.; Norton, T. R. Department of Pharmacology, University of Hawaii, unpublished results cited in ref 7.

(7) Finer, J.; Clardy, J.; Fenical, W.; Minale, L.; Riccio, R.; Battaile, J.; Kirkup, M.; Moore, R. E. *J. Org. Chem.* **1979**, *44*, 2044.

(8) (a) Hirschfeld, D. R.; Fenical, W.; Lin, G. H. Y.; Wing, R. M.; Radlick, P.; Sims, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 4049. (b) Fattorusso, E.; Magno, S.; Mayol, L.; Santacroce, C.; Sica, D.; Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C. *J. Chem. Soc., Chem. Commun.* **1976**, 575. (c) Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C.; Fattorusso, E.; Magno, S.; Mayol, L. *Ibid.* **1976**, 1024. (d) Minale, L.; Riccio, R. *Tetrahedron Lett.* **1976**, 2711. (e) Vanderah, D. J.; Faulkner, D. J., unpublished observations cited in ref 1c. (f) Faulkner, D. J.; Ravi, B. N.; Finer, J.; Clardy, J. *Phytochemistry* **1977**, *16*, 991.

(9) All structures in this paper represent single enantiomers with the indicated absolute stereochemistry.

(10) Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C. *Phytochemistry* **1979**, *18*, 1895.

(11) Danise, B.; Minale, L.; Riccio, R.; Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C.; Fattorusso, E.; Magno, S.; Mayol, L. *Experientia* **1977**, *33*, 413.

(12) Sun, H. H.; Waraszkiewicz, S. M.; Erickson, K. L.; Finer, J.; Clardy, J. *J. Am. Chem. Soc.* **1977**, *99*, 3516. See also: Bowden, B. F.; Coll, J. C.; Liyanage, N.; Mitchell, S. J.; Stokie, G. J.; van Altena, I. A. *Aust. J. Chem.* **1978**, *31*, 163.

(13) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4155.

(14) For preliminary reports of this work, see: Greene, A. E. *Tetrahedron Lett.* **1978**, 851; **1979**, 63.

(15) The interesting synthesis of dictyolene by Marshall and Wuts[16] appeared virtually simultaneously with our report of the synthesis of (+)-pachydictyol A.

(16) Marshall, J. A.; Wuts, P. G. M. *J. Am. Chem. Soc.* **1978**, *100*, 1627.

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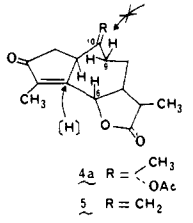
taceae. It has also been found in the digestive (midgut) glands of the sea hares *Aplysia depilans* and *Aplysia vaccaria*; however, this is undoubtedly a consequence of their algal diet[8d,e]. The structure of pachydictyol A, including absolute stereochemistry, was elucidated in 1973 by X-ray crystallographic analysis of its *p*-bromophenylurethane derivative[8a]. Interestingly, pachydictyol A exhibits antibiotic activity vs. *Staphylococcus aureus*.

Quite naturally, in planning the synthesis of this novel hydroazulene, particular concern was focused on its five contiguous asymmetric centers as well as on the generally unfavorable exo position of the double bond at C-10 (vide infra). Therefore, the fully elucidated, yet little used, crystalline dienone lactone **5**[17-19], synthesized from (−)-α-santonin (**3**) by Barton and co-workers in 1957 during their classic study of the photochemistry of santonin and related compounds[17], appeared to be an ideal point of departure. However, for synthetic purposes it seemed desirable first to ameliorate, if possible, the rather low (ca. 11%) yield reported for this transformation (**3** → **4b** → **5**, Scheme I).

O-Acetylisophotosantonic lactone (**4a**), prepared as early as 1886 by Cannizzaro and Fabris[21], could be easily obtained from α-santonin[22] in up to 36% yield on a large scale by direct crystallization using the procedure described by White, Eguchi, and Marx[23a]. Chromatographic purification of the material from the mother liquors furnished additional quantities of **4a**. Saponification of acetate **4a** as outlined by Arigoni and co-workers[20] afforded the crude alcohol **4b**, which, using thionyl chloride in pyridine,[17] was found to best engender the desired dienone lactone **5** at low temperatures in the presence of either THF (−45 °C) or dioxane (−20 °C) as a cosolvent. Under these conditions, *a single crystalline lactone* **5** was found, readily isolated in 63% yield by filtration over silica gel, thereby making this compound considerably more accessible than before for use in synthesis. It should be pointed out that the pleasingly high degree of selectivity observed in the dehydration **4b** → **5** stands in contrast to what is generally found with similar C-10 alcohols[2,24]. This includes, significantly, the C-10 alcohol derived from pachydictyol A epoxide, which affords in low yield the Δ^9 isomer of pachydictyol A and pachydictyol A in a 7:3 ratio, albeit with $POCl_3$ in pyridine.

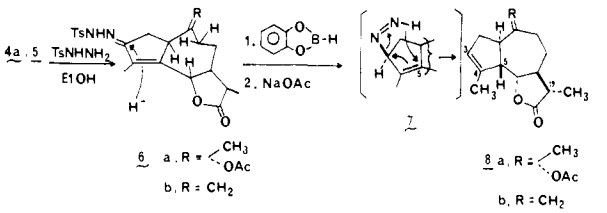
We now concentrated our efforts on the introduction of the C-3, C-4 double bond and the required C-5 β-H. From related work, it was known that conjugate reduction ($NaBH_4$, pyridine) of dienone lactone **5** and *O*-acetylisophotosantonic lactone (**4a**)[19] and



4a R = CH(CH3)OAc
5 R = CH2

hydrogenation (Pd/C, EtOAc) of the latter[23a] give "only" the corresponding cis-fused products. Furthermore, it had been shown that selective hydrogenation of **5** produces a β-methyl at C-10[18]. These results can be readily explained through an examination of Dreiding models, which indicate a steric encumbrance to β-face approach in both **4a** and **5** caused by the C-6 and C-9 hydrogens (or by the C-6,8 (and 10) hydrogens in the alternative conformation), thus making α-attack largely preferred in these molecules. It therefore seemed that it might be possible to take advantage of this high degree of stereoselectivity through the use of the then recently described "alkene walk", a reduction–olefin transposition process produced by sequential treatment of an α,β-unsaturated ketone with *p*-toluenesulfonylhydrazine, catecholborane, and sodium acetate[25].

Scheme II



Although the rather simple enones that had been studied precluded any completely confident predictions as to the stereochemical outcome of this mild reaction sequence, it did stand to reason that reduction of the tosylhydrazone **6b** (or **6a**) derived from **5** (or **4a**) would occur from the *less* hindered α side (vide supra) and, consequently, delivery of the C-5 hydrogen could be expected to take place on the *more* hindered β face of the molecule (as in **7**, Scheme II, assuming an intra- and not intermolecular mechanism to be operative[25]). This would nicely effect, in essentially a single operation, the introduction of both the double bond at C-3, C-4 and the β hydrogen at C-5.

Concordant with this reasoning, treatment of model enone **4a** sequentially, without purification, with tosylhydrazine, catecholborane, and sodium acetate gave highly stereoselectively in 70% yield a crystalline olefin lactone acetate **8a** (mp 117–118 °C; $[\alpha]_D$ −35°) that was distinctly different from the known cis-fused product (1α,5α-H's) (mp 66–67 °C, $[\alpha]_D$ +8°), an intermediate obtained by White and co-workers in their deacetoxymatricarin[23a] and achillin[23b] syntheses, although the spectral data were quite similar. In that ^1H NMR determination of the stereochemistry in such molecules is known to be rather unreliable[23], chemical confirmation that no changes had taken place in the molecule other than those indicated was desirable. This was satisfactorily obtained through the regeneration of enone **4a** from both the tosylhydrazone **6a** ($BF_3 \cdot OEt_2$, acetone–H_2O[26]) and the trisubstituted olefin **8a** (SeO_2, Jones[23a]).

With this encouragement, the above sequence of reactions was applied to dienone lactone **5** with very pleasing results. The desired Δ^3 olefin **8b** was produced stereoselectively in 55% overall yield. Since maintenance of the proper C-11 configuration was obviously vital to the success of the synthesis, the stereochemical homogeneity at this center in **8b** was verified through potassium *tert*-butoxide catalyzed epimerization[23b], which afforded a well-separated mixture of **8b** and its more polar (TLC, silica gel) C-11 epimer. Spectral and chromatographic comparison of crude **8b** with an unambiguously synthesized sample of the C-5 epimer[19] indicated that it contained at most a very minor amount of the cis-fused material. Similarly, NMR examination of the material in the mother liquors from the recrystallization of crude **8a** indicated only a very small amount of a *possible* isomeric compound. This remarkably high degree of stereoselectivity resulting in the introduction of a hydrogen from the *more* hindered side of the molecule coupled with the complete transposition of the double

(17) Barton, D. H. R.; de Mayo, P.; Shafiq, M. *J. Chem. Soc.* **1957**, 929. See also: Barton, D. H. R. *Helv. Chim. Acta* **1959**, *42*, 2604. Barton, D. H. R.; Levisalles, J. E. D.; Pinhey, J. T. *J. Chem. Soc.* **1962**, 3472. Barton, D. H. R.; Pinhey, J. T.; Wells, R. J. *Ibid.* **1964**, 2518. See also ref 20.

(18) Buchi, G.; Loewenthal, H. J. E.; Kauffman, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 3403.

(19) Edgar, M. T.; Greene, A. E.; Crabbé, P. *J. Org. Chem.* **1979**, *44*, 159.

(20) Arigoni, D.; Bosshard, H.; Bruderer, H.; Buchi, G.; Jeger, O.; Krebaum, L. J. *Helv. Chim. Acta* **1957**, *38*, 1732.

(21) Cannizzaro, S.; Fabris, G. *Chem. Ber.* **1886**, *19*, 2260.

(22) Previously prepared by total synthesis: Abe, Y.; Harukawa, T.; Ishikawa, H.; Miki, T.; Sumi, M.; Toga, T. *Proc. Jpn. Acad.* **1952**, *28*, 425; **1953**, *29*, 113; **1954**, *30*, 116, 119. *J. Am. Chem. Soc.* **1956**, *78*, 1422. Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1978**, *43*, 1086. Santonin is available from Sigma Chemical Co., St. Louis, Mo.

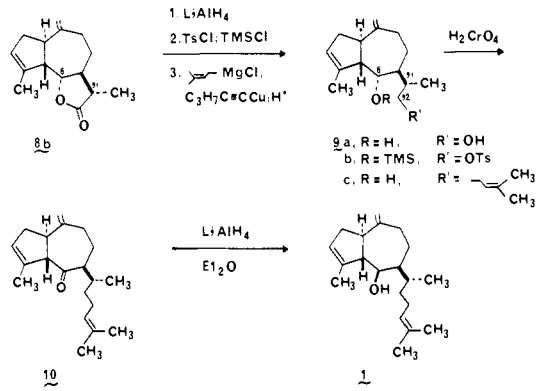
(23) (a) White, E. H.; Eguchi, S.; Marx, J. N. *Tetrahedron* **1969**, *25*, 2099. (b) Marx, J. N.; White, E. H. *Ibid.* **1969**, *25*, 2117.

(24) For example: (a) Shafizadeh, F.; Bhadane, N. R. *J. Org. Chem.* **1972**, *37*, 3168. (b) Piers, E.; Cheng, K. F. *Can. J. Chem.* **1970**, *48*, 2234. (c) Corbella, A.; Gariboldi, P.; Jommi, G.; Orsini, F.; Ferrari, G. *Phytochemistry* **1974**, *13*, 459. (d) Marshall, J. A.; Huffman, W. F.; Ruth, J. A. *J. Am. Chem. Soc.* **1972**, *84*, 4691. See, however, Maçaira, L. A.; Garcia, M.; Rabi, J. A. *J. Org. Chem.* **1977**, *42*, 4207.

(25) (a) Kabalka, G. W.; Yang, D. T. C.; Baker, Jr., J. D. *J. Org. Chem.* **1976**, *41*, 574. (b) Kabalka, G. W.; Baker, Jr., J. D.; Neal, G. W. *Ibid.* **1977**, *42*, 512. For related work using $NaBH_3CN$ and $NaBH_4$ with acid at elevated temperatures, see: Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662. Hutchins, R. O.; Kacher, M.; Rua, L. *J. Org. Chem.* **1975**, *40*, 923. Taylor, E. J.; Djerassi, C. *J. Am. Chem. Soc.* **1976**, *98*, 2275. Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299.

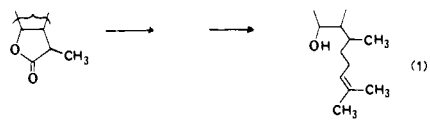
(26) Sacks, C. E.; Fuchs, P. L. *Synthesis* **1976**, 456.

Scheme III



bond (**4a** → **8a**, **5** → **8b**) offers compelling evidence, at least in these examples[27], for an intramolecular mechanism for the tosylhydrazone–catecholborane–sodium acetate version of the "alkene walk"[25]. The ability, as demonstrated above, to predict for this sequence the stereochemical outcome at the β carbon of the original enone system should prove generally useful[28].

At the time of this work, we were unable to find in the literature any effective procedures for "prenylating" lactones such as **8b** to afford the C-6 hydroxy, C-7 eight carbon unit arrangement found in pachydictyol A as well as in the numerous other diterpenes mentioned above (eq 1). In that the possibility of epimerization

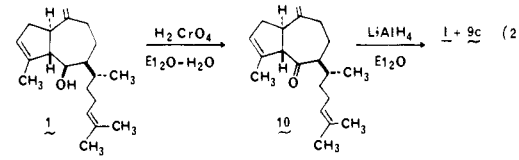


(1)

of the methyl group at C-11 was a primary concern, it was decided that **8b** should be reduced to the diol **9a** before attempting to elaborate the side chain (Scheme III). It was expected that a suitable method could be found for inverting the stereochemistry at C-6 after construction of the side chain had been completed[30].

A number of combinations of selective blocking, deblocking, and activating of the hydroxyl groups in **9a** were examined in attempting to arrive at the C-6 OH blocked to avoid internal displacement and the C-12 OH activated for joining with a prenyl unit. What was clearly the most efficient process found consisted of selective tosylation at the primary site with *p*-toluenesulfonyl chloride in pyridine at −30 °C followed by in situ trimethylsilylation (excess Me_3SiCl, −30 °C) at the less accessible C-6 position. The crude product **9b** from this one-pot sequence was then immediately subjected to copper-mediated coupling with prenylmagnesium chloride[31]. Using pentynylcopper[32] in diethyl ether at −30 to −40 °C the hydrogenolysis[16] of the C-12 tosylate was minimal and pure 6-*epi*-pachydictyol A (**9c**) could be obtained, following acid hydrolysis of the silyl ether, in a reasonable 30–35% overall yield for the entire sequence from lactone **8b**. With further modifications, however, this yield could undoubtedly be raised[33].

A simple solution to the final obstacle in the synthesis, the inversion of the configuration at C-6, was discovered in conjunction with the securing of a comparison sample of 6-*epi*-pachydictyol A (eq 2). Oxidation of a small quantity of naturally derived



(2)

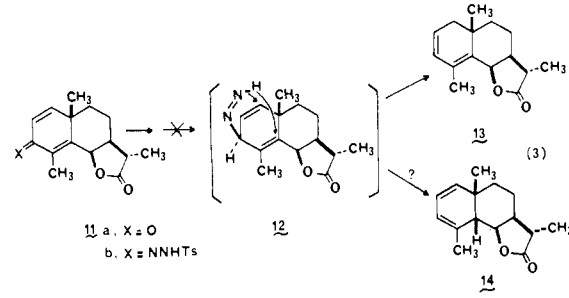
pachydictyol A (**1**) using the mild two-phase method described by Brown, Garg, and Liu[34] in order to minimize the likelihood of epimerization or double-bond conjugation gave dehydropachydictyol A (**10**)[8a], which, upon reduction with lithium aluminum hydride, regenerated highly stereoselectively pachydictyol A; only a very minor amount of 6-*epi*-pachydictyol A was formed. This result can be easily understood through steric considerations. Molecular models clearly indicate that the carbonyl is effectively shielded from β-attack by the C-8 and C-9 methylenes, assuming that the C-7 side chain is pseudoequatorial on this conformationally rather rigid cycloheptanone ring. In the alternative conformation, the bulky side chain occupies a pseudoaxial position, which would also serve to block the β face from hydride attack.

Thus, the synthesis of pachydictyol A could be easily completed. Two-phase chromic acid oxidation of 6-*epi*-pachydictyol A (**9c**) afforded the same ketone **10** as obtained above, which, as expected, upon reduction ($LiAlH_4$, Et_2O, −78 °C) again provided highly stereoselectively (ca. 90%) (+)-pachydictyol A ($[\alpha]_D$ +98°, lit.[8a] +106°; α-naphthylurethane mp 114–115 °C, lit.[8a] 114–115 °C), chromatographically and spectroscopically indistinguishable from authentic samples of the natural material kindly provided by Professors Fattorusso, Minale, and Sims.

(−)-Dictyolene. Erickson, Clardy, and co-workers in 1977 reported the isolation of a new diterpene alcohol, dictyolene, from the antibiotic extracts of the marine alga *Dictyota acutiloba* (Dictyotaceae), found off the Kahala and Ala Moana reefs (Oahu, Hawaii), and proposed the novel formula **2**[12]. This assignment was suggested from spectral studies on the limited quantities available of the unstable material[35] and through consideration that its biogenetic origin is probably in common with that of dictyoxepin, an unusual occidenol-like 4,5-dihydrooxepin isolated from the same extracts and completely elucidated (including absolute stereochemistry) by X-ray crystallography[12]. The proposed structure and relative stereochemistry of dictyolene were confirmed in 1978 by Marshall and Wuts[16] through their synthesis of racemic **2**.

The obvious "hybrid" relationship of the dictyolene structure with those of α-santonin and pachydictyol A, together with the scarcity of the natural material, prompted us to undertake the synthesis of this novel marine product.

Initial expectations were that the above tosylhydrazine–catecholborane–sodium acetate sequence when applied to 6-*epi*-α-santonin (**11a**) would result in stereoselective attack on the tosylhydrazone intermediate **11b** from the more accessible α side engendering diazene **12**, which would decompose sigmatropically to afford dienes **13** and **14**, with a probable preponderance of the undesired **13** from preferential hydrogen transfer to the less substituted β terminal (eq 3). The alternative plan in this



(3)

(27) See also: Kabalka, G. W.; Newton, Jr., R. J.; Chandler, J. H. *J. Chem. Soc., Chem. Commun.* **1978**, 726, and the dictyolene synthesis presented in this paper.

(28) It should be pointed out that metal reduction of **5** or of the corresponding hydroxy acid salt[29], as one might expect, produces hydrogenolysis at C-6 and therefore is not a viable method for introducing the trans ring fusion in the present work.

(29) Cf. Greene, A. E.; Muller, J. C.; Ourisson, G. *J. Org. Chem.* **1974**, *39*, 186.

(30) Alternatively, at least in principle, the synthesis could be repeated from 6-*epi*-α-santonin. See ref 17.

(31) Derguini-Boumechal, F.; Lorne, R.; Linstrumelle, G. *Tetrahedron Lett.* **1977**, 1181.

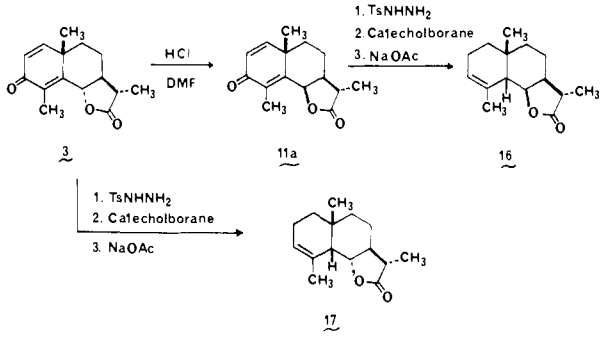
(32) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210. For a related coupling using this reagent, see: Meyers, A. I.; Roland, D. M.; Comins, D. L.; Henning, R.; Fleming, M. P.; Shimiza, K. *J. Am. Chem. Soc.* **1979**, *101*, 4732.

(33) For an alternative procedure for accomplishing this overall transformation, see ref 16.

(34) Brown, H. C.; Garg, C. P.; Liu, K. T. *J. Org. Chem.* **1971**, *36*, 387.

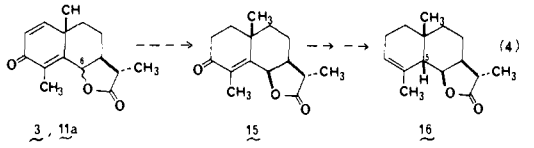
(35) Personal communication from Professor K. L. Erickson.

Scheme IV



3 11a 16 17

eventuality was to selectively hydrogenate the 1,2 double bond of 6-*epi*-α-santonin, or of α-santonin with subsequent C-6 isomerization[29,36], and then carry out the reduction–olefin transposition which would be expected to introduce a 5β-H and the Δ^3 half of the diene system (eq 4).



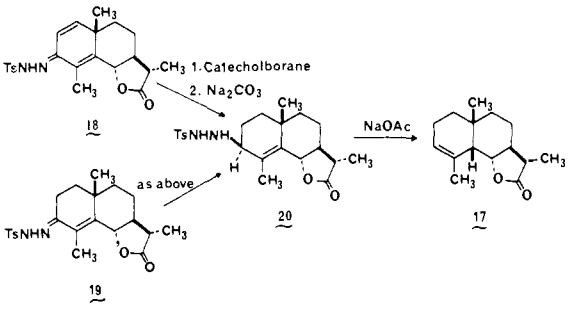
3, 11a 15 16 (4)

It was thus a pleasant surprise to find that when 6-*epi*-α-santonin (**11a**), secured by HCl–DMF treatment of α-santonin[36a], was subjected to the transformation sequence without isolation of intermediates, a single olefin **16**, mp 98–99 °C, was produced directly in 50% yield (Scheme IV). No meaningful amount of any diene, regardless of the relative quantities of reagents, or of any isomer was formed. Analogously, α-santonin (**3**) afforded very stereoselectively the known[29] eudesmanolide **17**, again to the exclusion of dienes[37]. In that it is known that the 1,2 double bond of santonin is susceptible to conjugate addition[38] and that tosylhydrazine can add 1,4 to certain enones quite effectively[39], the initial supposition was that reduction was occurring via such a conjugate addition followed by decomposition[39b] of the resulting tosylhydrazine–santonin adduct. This possibility was readily eliminated, however, by the isolation and characterization of the tosylhydrazone intermediate, clearly **18**, which on treatment with catecholborane–sodium acetate produced only the monoolefin **17**.

That conjugate reduction takes place during the next stage of the transformation was evidenced by the formation of allylic tosylhydrazine **20** from treatment of **18** with catecholborane, followed by rapid workup with aqueous sodium carbonate[40] (Scheme V). As expected, the 1,2-dihydro derivative **19** afforded the same allylic tosylhydrazine **20**, which underwent smooth decomposition in the presence of sodium acetate to afford olefin **17**.

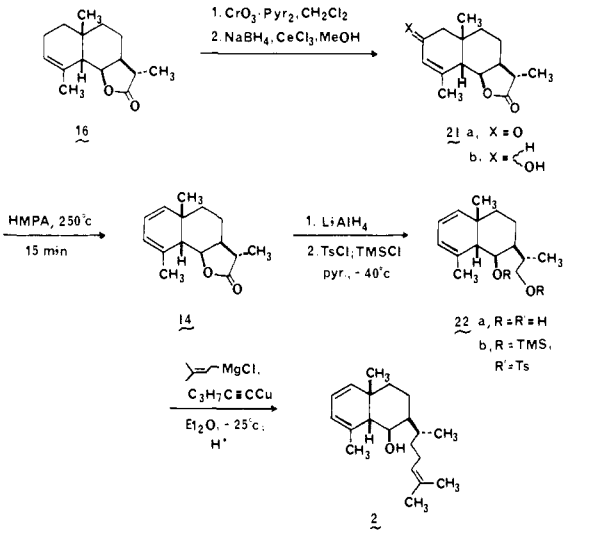
Completion of the cyclohexadiene system of dictyolene was achieved by first subjecting olefin **16** to Collins allylic oxidation[41], which very cleanly produced enone **21a**, mp 218–220 °C, in 71% yield (Scheme VI). Although base treatment of the corresponding

Scheme V



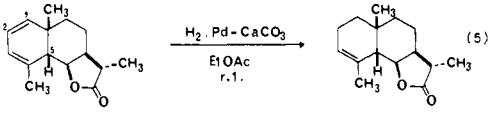
18 20 17 19

Scheme VI



16 21 a, X = O b, X = H, OH 14 22 a, R = R' = H b, R = TMS, R' = Ts 2

tosylhydrazone[42] did afford some of the required diene **14**, a higher yielding procedure was desired. It was found that 1,2 reduction of the enone **21a** using sodium borohydride–cerium chloride in methanol, a convenient and very effective method developed and used routinely in this laboratory for minimizing 1,4 reduction of enones[43], followed by dehydration of the resulting allylic alcohol **21b** with hot hexamethylphosphoric triamide (HMPA)[44] gave the nicely crystalline diene **14**, mp 100–101 °C, in 56% overall yield. Because there was a slight possibility that C-5 epimerization had taken place in the oxidation of **16** or that ring-fusion isomerization had occurred through reversible electrocyclic processes[45] during the high-temperature dehydration of **21b**, it was necessary to verify that the required stereochemistry had been maintained in transforming **16** to **14**. Fortunately, this could easily be achieved through selective reduction of the 1,2 double bond in diene **14**, which regenerated the original olefin **16** (eq 5).

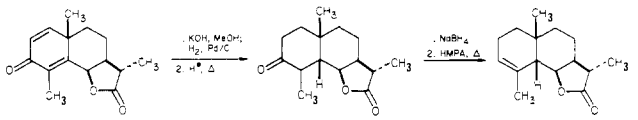


14 16 (5)

The completion of the synthesis required modification of the lactone of **14** to provide the C-6 hydroxyl, C-7 side chain of dictyolene. Application of the prenylation procedure used in the pachydictyol A synthesis was again successful and produced in 30–40% overall yield (−)-dictyolene (**2**), identified through spectral comparison with naturally derived dictyolene[46]. Although no

(36) (a) Piers, E.; Cheng, K. F. *Can. J. Chem.* **1968**, *46*, 377. (b) Sims, J. J.; Honwad, V. K.; Selman, L. H. *Tetrahedron Lett.* **1969**, 87. (c) Nakazaki, M.; Naemura, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1842.

(37) Additional support for the structure of **16** was obtained by an independent synthesis (in low overall yield). Cf. Cocker, W.; Gobinsingh, H.; McMurry, T. B. H.; Nisbet, M. A. *J. Chem. Soc.* **1962**, 1432.



11a 16

(38) See, for example, Edward, J. T.; Davis, M. J. *J. Org. Chem.* **1978**, *43*, 536, and references cited therein.

(39) (a) Kirmse, W.; Ruetz, L. *Justus Liebigs Ann. Chem.* **1969**, *726*, 30. (b) *Ibid.* **1969**, *726*, 36.

(40) Kikugawa, Y.; Kawase, M. *Synth. Commun.* **1979**, *9*, 49.

(41) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587.

(42) Shapiro, R. H. *Org. React.* **1976**, *23*, 405. Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717.

(43) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(44) Monson, R. S. *Tetrahedron Lett.* **1971**, 567. Spangler, C. W.; Hartford, T. W. *Synthesis* **1976**, 108.

(45) Woodward, R.B.; Hoffmann, R. "The Conservation of Orbital Symmetry"; Verlag Chemie: Weinheim Bergstr., West Germany, 1970. See also: Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965**, *87*, 5736. Miyashita, M.; Uda, H.; Yoshikoshi, A. *Chem. Commun.* **1969**, 1396.

optical rotation data is available for natural dictyolene[35], based on its likely biogenetic origin its absolute configuration should correspond to that of dictyoxepin[12], and thus, α-santonin.

In summary, pachydictyol A and dictyolene, diterpene alcohols from algae of the family Dictyotaceae, have been stereoselectively synthesized. It is expected that the basic approach will prove useful for the synthesis of other members of this novel, evergrowing class of marine natural products and for the synthesis of their analogues.

Experimental Section

Solvents were generally redistilled prior to use. Tetrahydrofuran, dioxane, and ether were distilled from lithium aluminum hydride, and hexamethylphosphoric triamide (HMPA) and pyridine were distilled from calcium hydride. Reaction products were isolated by addition of water followed by extraction with the solvent indicated and drying over anhydrous sodium sulfate or potassium carbonate.

Thin layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets which were visualized with molybdatophosphoric acid in ethanol. Merck 70–230 or 230–400 mesh silica gel 60 was employed for column chromatography. A Beckman Acculab 4 spectrophotometer was used to record IR spectra, and a JEOL PMX-60 spectrometer was used for the NMR spectra (Me_4Si as the internal reference). Mass spectra were obtained on an MS-30 AEI mass spectrometer (70 eV, direct insertion probe). Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Melting points were obtained using a Büchi-Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS, Lyon.

***O*-Acetylisophotosantonic Lactone (4a).** White's procedure was followed[23a]. A solution of 15.0 g (61 mmol) of α-santonin [Sigma, mp 171 °C, $[\alpha]^{24}_D$ −171° (*c* 1.7, $CHCl_3$)] in 220 mL of glacial acetic acid was irradiated under argon for 14 h using a Hanau TQ 150 high-pressure mercury arc lamp in a water-cooled quartz immersion well apparatus. The acetic acid was evaporated under reduced pressure and the resulting oil was dissolved in 25 mL of hot methanol, which was slowly cooled to −20 °C and then left overnight to afford 6.7 g (36%) of *O*-acetylisophotosantonic lactone (**4a**): mp 175–178 °C (lit. 175–177[17], 182–182.5[18], 176–177[20], 183[21], 180–181 °C[23a]); $[\alpha]^{24}_D$ + 48.8° (*c* 1.0, $CHCl_3$) [lit. $[\alpha]_D$ +58° (*c* 0.53, EtOH)[17], $[\alpha]_D$ +47° (*c* 0.8, $CHCl_3$)[20], $[\alpha]_D$ +59° (EtOH)[21], $[\alpha]^{24}_D$ +47.2° (*c* 0.86, $CHCl_3$)[23a]]; ^1H NMR (recrystallized sample, mp 180–181 °C, $CDCl_3$) δ 4.80 (br d, *J* = 9 Hz, 1 H), 4.13 (br s, 1 H), 2.00 (s, 3 H), 1.90 (t, *J* = 2 Hz, 3 H), 1.28 (d, *J* = 6 Hz, 3 H), 1.10 (s, 3 H); IR (Nujol) 1775, 1730, 1700, 1645 cm^{-1}. Additional **4a** (ca. 1 g/photolysis, mp 176–179 °C) could be secured by chromatography (SiO_2, EtOAc–hexane) of the oil from the pooled mother liquors from several runs, followed by recrystallization from methanol.

Dienone Lactone 5. *O*-Acetylisophotosantonic lactone (**4a**, 6.5 g, 21 mmol) was added to 1.2 L of 5% aqueous potassium hydroxide with stirring. After 1.25 h the reaction mixture was washed with ethyl acetate and then acidified with 18% hydrochloric acid and the product was isolated with ethyl acetate, providing 6.5 g of crude alcohol **4b**. This material was dissolved in 20 mL of tetrahydrofuran and cooled to −45 °C. A cold (−45 °C) solution of tetrahydrofuran (20 mL), pyridine (20 mL), and thionyl chloride (20 mL) was added followed by stirring for 10 min. After addition to cold water–ether, the reaction mixture was thoroughly extracted with ether, which was washed with aqueous sodium carbonate, water, and brine to furnish 4.5 g of an oil. This oil was purified by dry column silica gel chromatography using 30% ethyl acetate–hexane to afford 3.3 g (63%) of the dienone lactone **5**: mp 113.5–114.5 °C (EtOAc–hexane) (lit.[17] 113–115 °C); $[\alpha]^{21}_D$ + 329° (*c* 0.9, $CHCl_3$) [lit.[17] $[\alpha]_D$ +378° (*c* 1.21, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 4.93 (s, 1 H), 4.87 (m, 1 H), 4.78 (s, 1 H), 3.50 (m, 1 H), 1.87 (t, *J* = 2 Hz, 3 H), 1.26 (d, *J* = 6 Hz, 3 H); IR (Nujol) 3080, 1775, 1700, 1645 cm^{-1}.

Olefin Lactone 8a. A 920-mg (3.0 mmol) sample of enone ester **4a** and 750 mg (4.0 mmol) of *p*-toluenesulfonylhydrazine in 3.0 mL of absolute ethanol were heated at 80–85 °C (closed system) with stirring for 4 h under an argon atmosphere. Removal of the solvent under reduced pressure left a yellow solid which was dissolved in 9 mL of reagent-grade chloroform,[47] cooled to 0 °C, and treated under argon with 750 μL of catecholborane. After the mixture was stirred for 1 h at 0 °C and 1 h at room temperature, 3.0 g (22.1 mmol) of sodium acetate trihydrate was added and the mixture was heated at 60 °C for 1 h. After cooling, the mixture was filtered through 50 g of silica gel using chloroform to afford 743 mg of white solid. Recrystallization from methanol–water gave 616 mg (70%) of **8a** as white needles: mp 116–117 °C; $[\alpha]^{24}_D$ −35° (*c* 1.7, $CHCl_3$); ^1H NMR (CCl_4) δ 5.27 (br s, 1 H), 4.12 (pseudo-t, *J* = 9 Hz, 1 H), 1.90 (br s, 6 H), 1.33 (s, 3 H), 1.17 (*d*, *J* = 6 Hz, 3 H); IR (Nujol) 1765, 1725, 1650, 1250, 1170 cm^{-1}; mass spectrum *m/e* 232 (M^+ − AcOH).

The analytical sample was prepared by a second recrystallization from methanol–water, mp 117–118 °C. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27. Found: C, 69.57; H, 8.19.

In a separate experiment, the crude tosylhydrazone obtained from 120 mg (0.4 mmol) of enone ester **4a** was dissolved in 4 mL of acetone and 0.4 mL of water and treated with 76 μL of freshly distilled $BF_3{\cdot}OEt_2$[26]. After 4.5 days at room temperature the product was isolated with ether and recrystallized from methanol to provide **4a**, indistinguishable from the previously secured material. Enone ester **4a** was also regenerated from olefin lactone **8a** following White's procedure (ca. 5% yield)[23a].

Diene Lactone 8b. A 2.00-g (8.13 mmol) sample of dienone **5** and 2.00 g (10.7 mmol) of tosylhydrazine in 8 mL of absolute ethanol were heated under argon at 80 °C for 2 h followed by removal of the solvent under reduced pressure. The resulting foam was dissolved in 24 mL of reagent-grade chloroform[47] and treated at 0 °C under argon with 2.0 mL of catecholborane. After 1 h at 0 °C and 1 h at room temperature, 8.0 g (58.8 mmol) of sodium acetate trihydrate was added and the mixture was heated at 60–65 °C for 1 h. The cooled reaction mixture was filtered, the solid material was washed thoroughly with additional chloroform, and the chloroform solution was concentrated. Dry column chromatography of this material over silica gel using chloroform afforded 1.04 g (55%) of oily diene lactone **8b**: $[\alpha]^{30}_D$ +1.8° (*c* 1.7, $CHCl_3$); ^1H NMR (CCl_4) δ 5.31 (br s, 1 H), 4.83 (br s, 2 H), 4.23 (pseudo-t, *J* = 8 Hz, 1 H), 1.87 (br s, 3 H), 1.16 (d, *J* = 6 Hz, 3 H); IR (film) 3080, 3040, 1770, 1640, 1180, 1160, 990, 895 cm^{-1}; mass spectrum *m/e* 232 (M^+).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.49; H, 8.75.

Diol 9a. Diene lactone **8b** (523 mg, 2.2 mmol) was added slowly to 500 mg (13.2 mmol) of lithium aluminum hydride in 200 mL of diethyl ether. After the mixture was stirred overnight, 1.0 mL of water was cautiously added followed by 0.8 mL of 10% aqueous sodium hydroxide. The mixture was stirred for 30 min and then filtered through a pad of sodium sulfate. Removal of the solvent afforded 505 mg (95%) of oily diol **9a**: $[\alpha]^{22}_D$ +79° (*c* 1.7, $CHCl_3$); ^1H NMR (CCl_4) δ 5.33 (br s, 1 H), 4.6 (br s, 2 H), 3.83 (m, 1 H), 3.43 (m, 2 H), 1.67 (br s, 3 H), 0.83 (d, *J* = 6 Hz, 3 H); IR (film) 3080, 3040, 1640, 1035, 895 cm^{-1}; mass spectrum *m/e* 218 ($M^+ - H_2O$).

Anal. Calcd for $C_{15}H_{24}O_2{\cdot}^1/_4H_2O$: C, 74.81; H, 10.25. Found: C, 74.71; H, 10.21.

***6-epi*-Pachydictyol A (9c).** To 168 mg (0.71 mmol) of diol **9a** in 4.4 mL of dry pyridine cooled to −30 °C under argon was added 660 mg (3.5 mmol) of recrystallized *p*-toluenesulfonyl chloride. After the mixture was stirred for 2 h at −30 °C, 400 μL (3.2 mmol) of chlorotrimethylsilane was added. Ice chips were added after an additional 15 min at −30 °C and the reaction mixture was allowed to warm to room temperature. The product was isolated with ether in the usual manner to afford crude tosylate trimethylsilyl ether **9b** as a clear oil: ^1H NMR (CCl_4) δ 7.33 (AB q, *J* = 8 Hz, $\delta_a - \delta_b$ = 25 Hz, 4 H), 5.16 (br s, 1 H), 4.50 (br s, 2 H), 4.7–3.6 (m, 3 H), 2.36 (s, 3 H), 1.5 (br s, 3 H), 0.9 (d, *J* = 6 Hz, 3 H), 0.06 (s, 9 H); IR (film) 3480, 3080, 3040, 1655, 1640, 1600, 1370, 1250, 1190, 1180, 840 cm^{-1}.

To a mixture of 3-methyl-2-butenylmagnesium chloride (ca. 11.5 mmol) and 1-pentynylcopper[32] (200 mg, 1.53 mmol) in 6 mL of ether at −30 to −40 °C under argon was added the above tosylate **9b** in 3 mL of ether. The mixture was stirred for 2 h at −30 to −40 °C and then overnight at −20 to −15 °C. The resulting black mixture was poured into saturated aqueous ammonium chloride–ether which was then stirred for 1 h. The crude trimethylsilyl ether was isolated with ether and then immediately subjected to hydrolysis with 30 mL of an AcOH–THF–H_2O solution (3:2:1). After 45 min at room temperature, the solvents were evaporated at 30 °C under reduced pressure and the resulting oil was purified by dry column silica gel chromatography using 3% ethyl acetate–hexane to afford 67 mg (33%) of pure 6-*epi*-pachydictyol A (**9c**): $[\alpha]^{22}_D$ +70° (*c* 1.1, cyclohexane); ^1H NMR (CCl_4) δ 5.36 (br s, 1 H), 5.00 (br t, *J* = 7 Hz, 1 H), 4.55 (br s, 2 H), 3.84 (m, 1 H), 1.67, 1.59 (2 s, 9 H), 0.83 (d, *J* = 6 Hz, 3 H); IR (film) 3480, 3085, 3040, 1635, 1050, 1020, 880 cm^{-1}; mass spectrum *m/e* 288 (M^+).

The product was analyzed as its α-naphthylurethane derivative. Anal. Calcd for $C_{31}H_{39}O_2N_1$: C, 81.36; H, 8.59; N, 3.06. Found: C, 81.24; H, 8.63; N, 3.04.

(+)-Pachydictyol A (1). To 57 mg (0.20 mmol) of 6-*epi*-pachydictyol A (**9c**) in 1.5 mL of ether at 0 °C was added over 30 min with rapid stirring a total of 26 drops of chromic acid solution, also at 0 °C[34]. Ether

(46) Like the authentic material,[35] synthetic dictyolene proved to be rather unstable, undergoing substantial decomposition over a 2-week period while stored in ether under argon at −25 °C.

(47) This chloroform contained a small amount of ethanol.

and water were then added to the reaction mixture, the ether was separated, and the aqueous phase was extracted with an additional portion of ether. After being washed with aqueous sodium bicarbonate, water, and brine, the ether was dried over sodium sulfate and filtered. (A small quantity of the solution was freed of solvent: IR[8a] (film) 3080, 3040, 1705, 1640, 900 cm^{-1}.) The resulting ether solution (60 mL) was cooled to −77 °C and treated with 0.50 g of lithium aluminum hydride. After 3 h at −77 °C, 1 mL of water was added at 0 °C followed by 0.8 mL of 10% aqueous sodium hydroxide. Stirring was continued for an additional 30 min, after which sodium sulfate was added, the mixture was filtered, and the ether was evaporated under reduced pressure to afford 32 mg of clear oil. Dry column chromatography on 25 g of silica gel using 2.5% ethyl acetate–hexane gave 3 mg of 6-*epi*-pachydictyol A (**9c**) and 23 mg (40%) of pachydictyol A (**1**): $[\alpha]^{30}_D$ +98° (*c* 0.8, cyclohexane) [lit.[8a] $[\alpha]^{30}_D$ +106° (cyclohexane)]; ^1H NMR[8a] (CCl_4) δ 5.15 (br s, 1 H), 4.97 (br t, *J* = 7 Hz, 1 H), 4.60 (br s, 2 H), 3.76 (br d, *J* = 7 Hz, 1 H), 1.75 (s, 3 H), 1.67 (s, 3 H), 1.57 (s, 3 H), 0.95 (d, *J* = 5 Hz, 3 H); IR[8a] (film) 3500, 3080, 3040, 1655, 1640, 1445, 1380, 890 cm^{-1}; mass spectrum *m/e* 288 (M^+, 83%), 270 ($M^+ - H_2O$, 55%). The NMR, IR, and mass spectra were identical with those obtained from an authentic sample. An admixture of the synthetically and naturally derived compounds was chromatographically (TLC, silica gel) inseparable using a number of different solvent systems.

The α-naphthylurethane derivative was prepared conventionally, mp 114–115 °C (lit.[8a] 114–115 °C). Anal. Calcd for $C_{31}H_{39}O_2N$: C, 81.36; H, 8.59; N, 3.06. Found: C, 81.40; H, 8.61; N, 3.11.

6-*epi*-α-Santonin (11a). The procedure described by Piers and Cheng was followed[36a]. A solution of 10.0 g (40.7 mmol) of α-santonin in 100 mL of dry dimethylformamide containing 5% anhydrous hydrogen chloride was heated under argon at 90–95 °C for 3 h. After the mixture had stood overnight at room temperature, 75 mL of water was added and the solution was thoroughly extracted with chloroform. The combined extracts (~1 L) were washed three times with brine, once with sodium bicarbonate, and once with water, and then evaporated under reduced pressure (<50 °C). The resulting oil was filtered through 75 g of neutral alumina (activity 1) using toluene and the crude product was crystallized from ethyl acetate–hexane. The filtered material was washed once with ether to afford 4.7 g (47%) of 6-*epi*-α-santonin (**11a**) as prisms: mp 101–103 °C (lit. 103–104[36a], 102–105 °C[36c]); $[\alpha]^{21}_D$ −302° (*c* 1.0, CH_3OH) [lit. $[\alpha]^{23}_D$ −308° (*c* 0.9, CH_3OH)[36a], $[\alpha]^{10}_D$ −311° (*c* 1.5, C_2H_5OH)[36c]]; ^1H NMR[36a] ($CDCl_3$) δ 6.42 (AB q, *J* = 10 Hz, $\delta_a - \delta_b$ = 30 Hz, 2 H), 5.47 (d, *J* = 4 Hz, 1 H), 2.53 (q, *J* = 7 Hz, 1 H), 2.04 (s, 3 H), 1.37 (d, *J* = 8 Hz, 3 H), 1.27 (s, 3 H); IR[36a] (Nujol) 1770, 1655, 1625, 1185, 965, 940, 835 cm^{-1}.

Olefin Lactone 16. A solution of 2.50 g (10.2 mmol) of 6-*epi*-α-santonin (**11a**) and 5.00 g (26.8 mmol) of tosylhydrazine in 15 mL of absolute ethanol was heated under argon in a closed system at 83 °C for 2.5 h. The solvent was then evaporated under reduced pressure. The resulting yellow foam was dissolved in 30 mL of reagent-grade chloroform[47] at 0 °C under argon and treated with 3 mL of catecholborane. After 1 h at 0 °C and 1 h at room temperature, 15 g of sodium acetate trihydrate was added to the solution and the resulting mixture was heated at 60–65 °C for 1 h. After cooling to room temperature, the mixture was filtered through an admixture of sand and Celite and the filtrate was concentrated under reduced pressure. Dry chromatography of the resulting oil on silica gel using chloroform as the eluant gave 1.06 g of **16** after two recrystallizations from methanol–water. Chromatography of the material in the mother liquors afforded an additional 0.14 g (50% total yield) of olefin lactone **16**: mp 97.5–98.5 °C, raised to 99–99.5 °C by an additional recrystallization from methanol–water: $[\alpha]^{21}_D$ −127° (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.33 (br s, 1 H), 4.27 (dd, *J* = 7, 9 Hz, 1 H), 1.80 (br s, 3 H), 1.20 (d, *J* ≃ 6 Hz, 3 H), 0.90 (s, 3 H); IR (Nujol) 1765, 1650, 1310, 1170, 1080, 995, 975 cm^{-1}; mass spectrum *m/e* 234 (M^+).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.64; H, 9.24.

Olefin Lactone 17. α-Santonin (2.50 g, 10.2 mmol) was treated exactly as above, except that tosylhydrazone formation was effected over 10 h, to afford after recrystallization 1.15 g (48%) of olefin lactone **17**: mp 116–118 °C (hexane) (lit.[29] 119–121 °C); $[\alpha]^{21}_D$ −60° (*c* 0.1, $CHCl_3$) (lit.[29] $[\alpha]_D$ −65° (*c* 0.1, $CHCl_3$)); ^1H NMR[29] ($CDCl_3$) δ 5.39 (br s, 1 H), 4.33 (dd, *J* = 5, 10 Hz, 1 H), 1.67 (br s, 3 H), 1.20 (d, *J* = 7 Hz, 3 H), 1.10 (s, 3 H); IR[29] (Nujol) 3020, 1755, 1170, 1150, 1130, 1005 cm^{-1}; mass spectrum *m/e* 234 (M^+).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.03; H, 9.31.

Allylic Tosylhydrazine 20. Via Tosylhydrazone 18. α-Santonin (1.00 g, 4.1 mmol) and tosylhydrazine (2.00 g, 10.7 mmol) in 6 mL of absolute ethanol were heated at 83 °C for 10 h. Two recrystallizations of the crude tosylhydrazone from ethanol–water gave 1.21 g (72%) of **18** as short, white needles: mp ~242 °C dec; $[\alpha]^{21}_D$ +16° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.40 (AB q, *J* = 7 Hz, $\delta_a - \delta_b$ = 32 Hz, 4 H), 6.13 (AB q, *J* = 9 Hz, $\delta_a - \delta_b$ = 16 Hz, 2 H), 4.6 (br d, *J* = 10 Hz, 1 H), 2.38 (s, 3 H), 2.03 (s, 3 H), 1.22 (d, *J* = 6 Hz, 3 H), 1.18 (s, 3 H); IR (Nujol) 3220, 1765, 1660, 1590, 1165, 1025, 760 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_2SO_4$: C, 63.73; H, 6.33; N, 6.77; S, 7.73. Found: C, 64.00; H, 6.25; N, 6.88; S, 7.53.

A 414-mg (1.0 mmol) sample of tosylhydrazone **18** in 3 mL of reagent-grade chloroform[47] at 0 °C was treated under argon with 400 μL of catecholborane. After 1 h at 0 °C and 1 h at room temperature, 10 mL of chloroform and then 5 mL of 5% aqueous sodium carbonate were added to the solution. The chloroform layer was separated, washed once with brine, and dried over sodium sulfate. Removal of the solvent followed by two crystallizations from ethyl acetate–hexane (with considerable loss) provided 105 mg of tosylhydrazine **20**: mp 100–101 °C dec; $[\alpha]^{21}_D$ −20° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.43 (AB q, *J* = 7 Hz, $\delta_a - \delta_b$ = 29 Hz, 4 H), 4.50 (br d, *J* = 8 Hz, 1 H), 3.00 (br s, 1 H), 2.38 (s, 3 H), 1.77 (s, 3 H), 1.17 (d, *J* = 7 Hz, 3 H), 1.06 (s, 3 H); IR (Nujol) 3260, 3040, 1755, 1600, 1335, 1165, 1035, 820 cm^{-1}.

Anal. Calcd for $C_{22}H_{30}N_2SO_4$: C, 63.13; H, 7.22; N, 6.69; S, 7.65. Found: C, 63.27; H, 7.35; N, 6.66; S, 7.76.

Via Tosylhydrazone 19. 1,2-Dihydro-α-santonin[29] (1.0 g, 4.0 mmol) and 1.5 g (8.1 mmol) of tosylhydrazine in 6 mL of absolute ethanol were heated in a closed system at 85 °C for 2 h. The precipitated material was filtered and recrystallized from hot ethanol–water to provide 1.54 g (92%) of tosylhydrazone **19** as white needles: mp 225 °C dec; $[\alpha]^{21}_D$ +192° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38 (AB q, *J* = 8 Hz, $\delta_a - \delta_b$ = 33 Hz, 4 H), 4.5 (br d, *J* = 8 Hz, 1 H), 2.37 (s, 3 H), 2.00 (br s, 3 H), 1.22 (d, *J* = 7 Hz, 3 H), 1.10 (s, 3 H); IR (Nujol) 3230, 1760, 1595, 1165, 1020, 910 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}N_2SO_4$: C, 63.44; H, 6.77; N, 6.73; S, 7.70. Found: C, 63.49; H, 6.72; N, 6.71; S, 7.63.

Catecholborane reduction of 416 mg (1.0 mmol) of tosylhydrazone **19** was carried out as described above for **18** and afforded after recrystallization 278 mg (67%) of tosylhydrazine **20**, identical by IR, NMR, TLC, melting point, and mixture melting point with that previously obtained.

Olefin **17** was produced in 72% yield on heating 100 mg of **20** with excess sodium acetate trihydrate in chloroform at 55 °C overnight followed by purification on silica gel. It could also be secured in 75% yield from tosylhydrazone **19** using catecholborane followed by sodium acetate, as described above.

Enone Lactone 21a. Allylic oxidation of olefin **16** was carried out using Dauben's procedure[41]. To 1.05 g (4.49 mmol) of olefin **16** in 300 mL of dry methylene chloride was added 23 g of the chromium trioxide–pyridine complex. After being stirred for 11 h at room temperature, the mixture was poured into ether, which was washed six times with sodium bicarbonate solution, twice with 10% hydrochloric acid, once again with sodium bicarbonate, and then with water and brine. After drying over potassium carbonate, the solvent was removed and the product was recrystallied from ethyl acetate–hexane to afford in two crops 790 mg (71%) of enone lactone **21a** as prisms: mp 218–220 °C; $[\alpha]^{21}_D$ −95° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.84 (br s, 1 H), 4.30 (dd, *J* = 6, 9 Hz, 1 H), 2.10 (d, *J* = 1.5 Hz, 3 H), 1.22 (d, *J* = 6 Hz, 3 H), 1.02 (s, 3 H); IR (Nujol) 3030, 1760, 1655, 1620, 1170, 995 cm^{-1}; mass spectrum *m/e* 248 (M^+).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.73; H, 8.11.

Diene Lactone 14. A 350-mg (1.41 mmol) sample of enone lactone **21a** in 35 mL of methanol containing 700 mg (1.88 mmol) of cerium(III) chloride heptahydrate was treated with 350 mg (9.25 mmol) of sodium borohydride over a 1-min period. After being stirred for an additional 5 min, the reaction mixture was worked up in the usual manner to give 350 mg of crude allylic alcohol **21b** as a foam: IR (film) 3400, 3020, 1765 cm^{-1}. Crude **21b** dissolved in 9 mL of hexamethylphosphoric triamide under argon was heated at 245–255 °C for 15 min. After cooling, the reaction mixture was poured into ether, which was washed three times with 10% aqueous hydrochloric acid, once with saturated sodium bicarbonate, and once with brine. The ether was dried over potassium carbonate and then evaporated, leaving 310 mg of crude diene. Purification of this material by dry column silica gel chromatography using chloroform as the eluant gave 184 mg (56%) of pure diene lactone **14**: mp 100–101 °C (CH_3OH–H_2O); $[\alpha]^{21}_D$ −406° (*c* 1.0, $CHCl_3$); ^1H NMR (CCl_4) δ 5.80 (dd, *J* = 4, 9 Hz, 1 H), 5.67 (m, 1 H), 5.20 (br d, *J* = 9 Hz, 1 H), 4.07 (dd, *J* = 6, 9 Hz, 1 H), 1.97 (s, 3 H), 1.13 (d, *J* = 6 Hz, 3 H), 0.90 (s, 3 H); IR (Nujol) 3040, 1770, 1655, 1170, 1000, 980 cm^{-1}; UV (CH_3OH) 265 nm (ε 4700); mass spectrum *m/e* 232 (M^+).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.30; H, 8.70.

A sample of diene lactone **14** was hydrogenated (EtOAc, 10% Pd/$CaCO_3$), cleanly affording olefin **16**, indistinguishable by melting point

and spectral and chromatographic comparison from the previously obtained material.

Diene Diol 22a. A 100-mg (0.43 mmol) sample of diene lactone **14** and 100 mg (2.63 mmol) of lithium aluminum hydride in 10 mL of ether were stirred overnight at room temperature. Water (200 μL) and 10% sodium hydroxide (160 μL) were added. After approximately 30 min, the mixture was filtered through a pad of sodium sulfate and the ether was evaporated, leaving 100 mg (98%) of diene diol **22a**, which was sublimed (75 °C, 0.01 mm) for characterization: mp 100–103 °C; $[\alpha]^{24}_D$ −279° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.77 (dd, *J* = 5, 9 Hz, 1 H), 5.68 (m, 1 H), 5.13 (d, *J* = 9 Hz, 1 H), 4.3–3.3 (complex m, 5 H), 1.90 (s, 3 H), 0.92 (s, 3 H), 0.90 (d, *J* = 5 Hz, 3 H); IR (Nujol) 3200, 3020, 1655, 1105, 1085, 1065, 1045, 1025, 975, 900, 875 cm^{-1}; mass spectrum *m/e* 236 (M^+).

Anal. Calcd for $C_{15}H_{24}O_2 \cdot {}^1/_4H_2O$: C, 74.80; H, 10.25. Found: C, 74.89; H, 10.05.

(−)-Dictyolene (2). To 50 mg (0.21 mmol) of diene diol **22a** in 1.45 mL of dry pyridine cooled to −40 °C under argon was added 200 mg (1.0 mmol) of recrystallized *p*-toluenesulfonyl chloride. After the mixture was stirred for 2 h at −30 to −40 °C, 110 μL (0.87 mmol) of chlorotrimethylsilane was added. Ice chips were then added after an additional 15 min at −30 to −40 °C and the reaction mixture was allowed to warm to room temperature. The reaction product was isolated with ether in the usual manner to afford crude tosylate trimethylsilyl ether **22b** as an oil: IR (film) 3030, 1650, 1600, 1365, 1250, 1190, 1175, 1095, 1055, 840 cm^{-1}.

To a mixture of 3-methyl-2-butenylmagnesium chloride (ca. 3 mmol) and 1-pentynylcopper[32] (50 mg, 0.38 mmol) in 2 mL of ether at −30 to −40 °C under argon was added the above tosylate **22b** in 0.5 mL of ether. The mixture was stirred for 2.5 h at −20 °C and then poured into saturated aqueous ammonium chloride–ether and stirred for 15 min. The crude trimethylsilyl ether was isolated with ether and then subjected to hydrolysis using 15 mL of a AcOH–THF–H_2O solution (3:2:1). After 45 min at room temperature, the solvents were evaporated at 25 °C under reduced pressure and the resulting oil was purified by dry column silica gel chromatography using 1% ethyl acetate–hexane to give 23 mg (38%) of dictyolene (**2**): $[\alpha]^{23}_D$ −154° (*c* 0.8, $CHCl_3$); ^1H NMR[12] (250 MHz, $CDCl_3$) δ 5.70 (dd, *J* = 5.5, 9 Hz, 1 H), 5.65 (m, 1 H), 5.26 (d, *J* = 9 Hz, 1 H), 5.12 (t, *J* = 7 Hz, 1 H), 4.06 (br dd, *J* = 2.5, 5 Hz, 1 H), 2.04 (d, *J* = 5 Hz, 1 H), 1.87 (s, 3 H), 1.70 (s, 3 H), 1.61 (s, 3 H), 1.03 (s, 3 H), 0.91 (d, *J* = 6.5 Hz, 3 H); IR[12] (film) 3030, 1655, 1640, 1450, 1375, 1025, 985 cm^{-1}; UV[12] (C_2H_5OH) 206 nm (ε 4400), 266 (4000); mass spectrum *m/e* 288 (M^+, 18%).

Comparison of the above spectra with those kindly provided by Professor Erickson of naturally derived dictyolene, in particular the 250- and 270-MHz NMR spectra, unambiguously confirmed the identity of the synthetically derived material.

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Long-Distance Intramolecular Electron Transfer in a Macrocyclic Crown Ether, a Thermoneutral, Nonadiabatic Process

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Abstract: The anion radical of 19,22,23,26-tetracyano-2,3:11,12-dibenzo-1,4,7,10,13,16-hexaoxaoctadeca-2,11-diene (I) was generated in solution by both electrolytic and chemical reduction. Electrochemistry and ESR and optical spectroscopies were employed to characterize the structure, spin distribution, ion pairing, and intramolecular electron transfer kinetics of $I^{-}\cdot$. Under most conditions the evidence is consistent with unpaired electron spin localized on one of the two equivalent aromatic rings (a_N = 1.86 G, a_H = 1.45 G, *g* = 1.0027). However, when $I^{-}\cdot$ was present as an ion pair with Na^+ or K^+ in dimethoxyethane, intramolecular electron transfer became detectable on the time scale of ESR. The Arrhenius parameters for this process (E_a = 1.4 kcal/mol, $A = 4.6 \times 10^7$ s^{-1}) are exceptionally small. The results are interpreted in terms of electrostatic contributions to the energetics and a nonadiabatic mechanism, whereby very weak electronic coupling between reactant and product wave functions depresses the time-average probability of electron transfer in the activated complex. (Spectroscopic results are also presented for anion radicals of the related molecules II and III and for the diradical dianion $I^{2-}\cdot$.)

Introduction

Electron transfer between species of comparable electron affinity does not require intimate interaction of the reaction partners. Weak mixing between the reactant and product wave functions is sufficient to permit transfer to occur on virtually every excursion of the nuclei through the activated complex configuration. In order for this to be the case, interaction between donor and acceptor orbitals need only be a very small perturbation, orders of magnitude less than typical bond energies. This requirement can be easily met by the vast majority of examples which have been studied, and this is why the adiabatic description of electron transfer has met with substantial success.[2,3]

It is of interest to know how electron-transfer reactions behave in the limit of extremely feeble electronic coupling. For example, is there a threshold below which the mechanism changes qualitatively? Are nonadiabatic mechanisms operative in solution? Considerable effort has been devoted to theoretical characterization of this situation. However, with the possible exception of highly exothermic reactions, experimental evidence remains ambiguous.[2a]

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