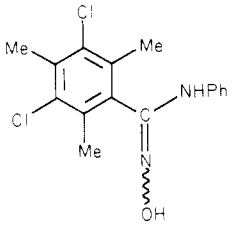

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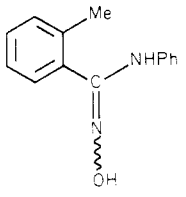
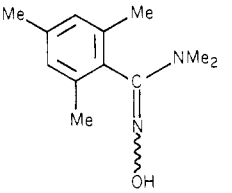


2

ration about the C=N double bond. The former phenomenon seemed more likely than the latter since the thermal *E,Z* isomerization in oximino compounds was currently considered a very high energy process as substantiated by the activation energy of 32 kcal/mol determined for a typical case:[3] this value considerably exceeds the 20 kcal/mol observed for **1** and **2**. However, doubts were advanced in view of the possibility that the presence of the heteroatom could lower the *E,Z* barrier to the change, as exceptionally observed for other oximino compounds.[4] This doubt has been reinforced by the recent work by Dignam and Hegarty,[5] who in fact reported the rate constants for the *E,Z* isomerization of a series of amidoximes from which activation energies as low as 21–25 kcal/mol can be calculated.

(3) Vassian, E. G.; Murmann, R. K. *J. Org. Chem.* **1962**, *27*, 4309.
(4) McCarty, C. G. In "The Chemistry of the Carbon–Nitrogen Double Bond"; Patai, S., Ed.; Interscience: New York, 1969; p 363.
(5) Dignam, K. J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 2* **1979**, 1437.

In order to clarify this point we have studied the ^{13}C NMR spectrum of amidoxime **3** in CD_2Cl_2 as a function



3

of temperature; this compound belongs to the same series of benzamidoximes **1** and **2** and has been properly built up to allow unambiguous assignments of the stereodynamic processes. Since at room temperature we observed one signal for each set of equivalent methyls, this indicates that the C—N rotation is fast and that we are dealing with one of the two configurational isomers *E* or *Z* or, less likely, that the *E,Z* isomerization is very fast. On lowering the temperature, we could detect two signals of equal intensities for the NMe_2 methyl, whereas the ortho methyls of the mesityl group remained equivalent. This clearly proves that the C—NMe_2 rotation has been locked; the energy barrier calculated from the line-shape analysis was 11.2 kcal/mol, a much lower value than that obtained for the internal motion in **1** and **2**. Consequently, we are now convinced that *E,Z* isomerization, rather than rotation about the C—N bond, was the phenomenon observed also in benzamidoximes **1** and **2**.

Registry No. **1**, 27886-91-5; **2**, 78965-29-4; **3**, 6157-67-1.

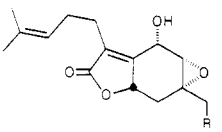
Communications

A Common Strategy for Construction of the Paniculides (A–C): Total Synthesis of Paniculide A

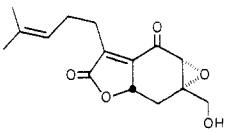
Summary: We disclose here the first total synthesis of (±)-paniculide A.

Sir: The paniculides A–C, highly oxygenated sesquiterpenes, were isolated in 1968 by Overton and co-workers[1] from callus cultures of *Andrographis paniculata*, during the course of phytochemical studies[2] both with intact plants[3] and the derived tissue cultures. While these novel sesquiterpenes have been known for well over a decade, their structures have yet to be confirmed either by X-ray analysis or by total synthesis; currently they rest on elemental composition data in conjunction with spectral properties, most notably high-field NMR data.[1] Indeed, to the best of our knowledge there exists only one report directed at construction of the basic carbocyclic skeleton; this is the work of Jacobi.[4]

In this communication we report the *first* total synthesis of (±)-paniculide A (**1**). We note in advance that our strategy is short, highly efficient, and stereocontrolled; furthermore, it serves for the *first time* to confirm the structural assignments of the paniculides.



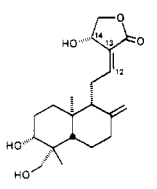
1, Paniculide A (R = H)
2, Paniculide B (R = OH)



3, Paniculide C

At the outset, we set as an overall goal the development of a common synthetic strategy that would in turn afford paniculides A, B, and C.[5] Ideal in this regard appeared to be bicyclic ketones **4a** and **4b**, both presumably readily available after modest functional group manipulation of

(1) A. J. Allison, D. N. Butcher, J. D. Connolly, and K. H. Overton, *Chem. Commun.*, 1493 (1968).
(2) D. N. Butcher and J. D. Connolly, *J. Exp. Bot.*, **22**, 314 (1971).
(3) Recently, we have successfully completed a single-crystal X-ray analysis of andrographolide, the major diterpenoid metabolite of the parent plant; unpublished results of B. H. Toder and P. J. Carroll. The structure including stereochemistry was found to be i:



i

(4) P. A. Jacobi and T. Craig, *J. Am. Chem. Soc.*, **100**, 7748 (1978); also see P. A. Jacobi, D. G. Walker, and I. M. A. Odeh, *J. Org. Chem.*, **46**, 2065 (1981).
(5) Paniculide C (**3**) has been prepared from paniculide B (**2**) via mild oxidation; see ref 1.

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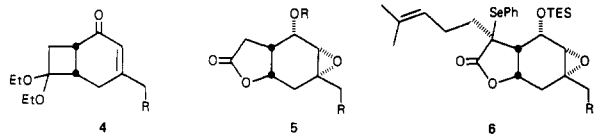
an initially generated [2 + 2] photoadduct between an appropriate cyclohexenone and 1,1-diethoxyethylene.

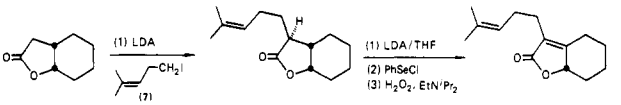


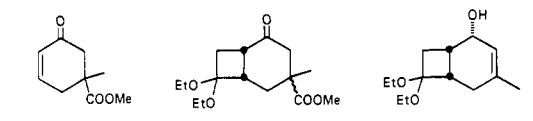
a, R = H
b, R = OH

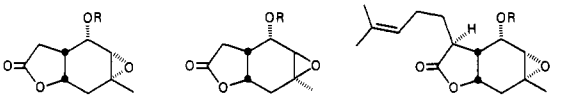
Central to this scenario is the concave–convex nature of photoadduct **4**, the latter providing the needed stereochemical bias required to introduce the epoxide oxygen relative to the protected cyclobutanone ring. In turn the cyclobutanone was anticipated to serve as a latent γ-lactone (Baeyer–Villiger oxidation)[6] and eventually as the butenolide ring system.[7] Final introduction of both side chain and unsaturation then appeared straightforward, assuming, of course, that the regiochemical problem associated with unsaturation introduction could be solved. Our plan here called for utilization of the Reich[9]–Sharpless[10] phenylselenation oxidative–elimination protocol.[11]

To assure that our penultimate strategy was indeed viable, as well as to select the optimal electrophile for introduction of the unsaturated side chain, we completed the illustrated model study.[12] The electrophile of choice proved to be 2-methyl-5-iodo-2-pentene (**7**).[13] Subsequent oxidative–elimination of the derived selenoxide resulted, as anticipated, in the butenolide[12] possessing the requisite endo unsaturation; the overall yield was 72%.

With the model study complete, we initiated synthesis of paniculide A with enone **8**.[14] Taking advantage of the known propensity of cyclic enones to undergo photochemical [2 + 2] cycloaddition with 1,1-diethoxyethylene in a regiocontrolled manner (i.e., head to tail),[15] irradiation of a mixture of enone **8** (0.33 M) and diethoxyethylene (1.0 M) in benzene afforded bicyclic ketone **9**[12] in 84% yield as a mixture of diastereomers. This photochemical transformation was most conveniently carried out on a 10–20-g scale, employing the standard Hanovia 450-W mercury arc fitted with Pyrex filter. Subsequent saponification (87% yield) followed by the Kochi–McMurry $Pb(OAc)_4$[16] induced oxidative–decarboxylation gave **4a**[12] as a single compound in 40–45% yield.







a, R = H
b, R = TES

For the proposed stereocontrolled introduction of the epoxide oxygen, the stage was set by reduction of **4a** with $NaBH_4$/0.4 M Ce^{3+} in MeOH[16] to afford a single allylic alcohol **10**.[12] Subsequent deketalization [HOAc/THF/H_2O (3:2:2), 98%] and oxidation with 3 equiv of *m*-CPBA in CH_2Cl_2 containing 3.2 equiv of $NaHCO_3$ afforded a 3:1 mixture[18] of epoxy lactones **11a** and **12a**,[12] respectively in 84% yield, readily separable by flash chromatography [silica gel/Et_2O–EtOAc (3:2)]. As anticipated, the major isomer **11a** (mp 135–136 °C) derived via C(8)-hydroxyl directed endo epoxidation (vide infra).

Having set the requisite stereochemical features of paniculide A, all that remained was introduction of the C(8) side chain and unsaturation at C(6,7). Toward this end, the hydroxyl group in **11a** was first protected as the triethyl silyl (TES) ether [TESCl/Et_3N/DMAP/CH_2Cl_2][19] to afford **11b**.[12] Subsequent alkylation [LDA/THF/−78 °C] with **7** afforded **13**[12] in 71% as a crystalline solid (mp 60–61 °C).

(6) For similar exploitation of a cyclobutanone ring as a latent γ-lactone, see Grieco's elegant total syntheses of ivangulin and eriolanin; P. A. Grieco, T. Oguri, C. J. Wang, and E. Williams, *J. Org. Chem.*, **42**, 4113 (1977), and P. A. Grieco, T. Oguri, S. Gilman, and G. T. DeTitta, *J. Am. Chem. Soc.*, **100**, 1616 (1978).

(7) More specifically, reduction of **4** from the convex surface and subsequent directed epoxidation (ca. with *m*-CPBA)[8] were expected to effect (hopefully in one step) both the required stereocontrolled introduction of the epoxide and transformation of the cyclobutanone ring to the required γ-lactone.

(8) H. B. Henbest, *Proc. Chem. Soc.*, **75**, 159 (1963); P. Chamberlain, M. L. Roberts, and G. H. Whitham, *J. Chem. Soc. B*, 1374 (1970), and references cited therein.

(9) H. J. Reich, I. L. Reich, and J. M. Renga, *J. Am. Chem. Soc.*, **95**, 5813 (1973).

(10) K. B. Sharpless and R. F. Lauer, *J. Am. Chem. Soc.*, **95**, 2697 (1973).

(11) For success two prerequisites would be mandatory. First the hydrogen at C(7) and the phenyl selenoxide group, respectively, in **6** must have a cis disposition. To set this stereochemistry, we again anticipate taking advantage of the concave–convex nature of substrate. Second, thermal elimination of PhSeOH must proceed to afford the endo and not the exo olefin. Here, as first pointed out by Trost, the dipole moment of the lactone carbonyl and that of the selenoxide (in his case sulfoxide) will align in such a fashion as to direct the oxygen of the selenoxide toward the endo β-hydrogen; see B. M. Trost, T. N. Salzmann, and K. Hiroi, *J. Am. Chem. Soc.*, **98**, 4887 (1976); for selenium examples, see: P. A. Grieco and M. Miyashita, *J. Org. Chem.*, **39**, 120 (1974); P. A. Grieco, C. S. Pogonowski and S. Burke, *ibid.*, **40**, 542 (1975).

(12) (a) The structure assigned to each new compound was in accord with its infrared and 220-, 250-, or 360-MHz NMR spectra. Analytical samples of all new compounds, obtained by recrystallization or chromatography (LC or TLC), gave satisfactory C and H combustion analysis within 0.4% and/or appropriate parent ion identification by high-resolution mass spectrometry. (b) All yields recorded here are based upon isolated material which was >97% pure. The IR and 250-MHz NMR spectral data of representative intermediate are recorded below. **4a**: IR (CCl_4) 1660 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.08 (t, *J* = 3.1 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 1.94 (s, 3 H), 2.32 (m, 2 H), 2.50 (m, 2 H), 2.27 (m, 2 H), 3.06 (t, J = 8 Hz, 1 H), 3.40 (m, 4 H), 5.88 (bs, 1 H). **11a**: IR (Nujol) 3450 (s), 1760 (b); NMR (acetone-d_6) δ 1.31 (s, 3 H), 2.03 (m, 1 H), 2.14 (d, *J* = 7.2, 2 H), 2.36 (dd, *J* = 10.8, 18 Hz, 1 H), 2.84 (dd, *J* = 5.4, 18 Hz, 1 H), 3.12 (m, 2 H), 4.31 (d, *J* = 7.2, 1 H), 4.48 (m, 1 H).

(13) W. Biernacki and A. Gdula, *Synthesis*, 1, 37 (1979); also see M. Julia, S. Julia, and R. Guégan, C. R. *Acad. Sci.*, **248**, 820 (1959); M. Julia, S. Julia and R. Guégan, *Bull. Soc. Chim. Fr.*, 1072 (1960).

(14) For previous preparations of enone **8** see: (a) D. K. Banerjee and V. Sarendranath, *Indian J. Chem.*, **13**, 201 (1975); (b) A. S. Kende, D. Constantinides, S. J. Lee, and L. Liebeskind, *Tetrahedron Lett.*, 405 (1975). For large-scale preparation of enone **8** we have employed the Birch–Marshall reductive–alkylation [see: J. A. Marshall and P. G. M. Wuts, *J. Org. Chem.*, **42**, 1794 (1977)] of *m*-anisic acid followed by Fisher esterification to be preferable.

(15) E. J. Corey, J. Bass, R. LeMahieu, and R. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964).

(16) J. D. Bacha and J. K. Kochi, *Tetrahedron*, **24**, 2215 (1968); J. E. McMurry and L. C. Blaszczak, *J. Org. Chem.*, **39**, 2217 (1974).

(17) J. L. Luche, *J. Am. Chem. Soc.*, **100**, 2226 (1978): for an example exploiting the stereoselectivity of the $NaBH_4/Ce^{3+}$ protocol, see P. A. Wender and J. C. Lechleiter, *J. Am. Chem. Soc.*, **102**, 6340 (1980). We have also effected the reduction of enone **8** with DIBAL; again allylic alcohol **10** was obtained as the sole product.

(18) A similar 3:1 diastereomeric mixture of epoxy ketones (**11a** and **12a**) was produced upon treatment of **10** with $VO(AcAc)_2$ and *tert*-butyl hydrogen peroxide [K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, **95**, 6136 (1973)] followed by hydrolysis [3:2:2 AcOH/THF/H_2O (v/v/v)] and *m*-CPBA oxidation.

(19) T. W. Hart, D. A. Metcalfe, and F. Scheinmann, *Chem. Commun.*, 156 (1979); also see: S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 99 (1979).

With ample quantities of **13** assured, we turned to the final task, introduction of the requisite C(6,7) unsaturation. Thwarted initially by the inability of LDA/THF to effect deprotonation at a temperature commenserate with survival of the derived enolate, we examined a number of related amide bases. To our delight treatment of **13** with 1.2 equiv of lithium tetramethylpiperidine (LiTMP) first at −10 °C for 1.5 h, then at 0 °C for 0.5 h with addition of 3 equiv of HMPA, and then at −20 °C with addition of 2.0 equiv of phenylselenyl chloride in THF (2 h), afforded the desired exo selenide (**6**)[12] in 49% yield after flash chromatography [silica gel/hexane–ether (3:1)]. Subsequent oxidative-elimination [$NaIO_4$ (excess)/H_2O/MeOH] with concomitant removal of the TES protecting group afforded (±)-paniculide A (**1**) in 72% yield after thin-layer chromatography [silica gel/ether]. That indeed (±)-paniculide A was in hand was confirmed by careful comparison of the IR, high-field NMR (250 MHz), and TLC retention characteristics (three solvent systems) to those of an authentic sample of paniculide A kindly provided by Professor Overton.[20]

In summation, the first total synthesis of (±)-paniculide A (**1**) has been achieved in stereocontrolled fashion. The approach proved to be both economical, proceeding in ten steps, and efficient, 4.2% overall yield from enone **8** (average yield/step, 73%). Studies to improve this sequence as well as to effect the total synthesis of paniculides B and C paralleling the above strategy will be reported in due course.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (Institute for General Medical Sciences) through Grant No. GM-24680. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalyses and Dr. G. Furst of the University of Pennsylvania for aid in recording and interpretation of the high-field NMR data.

(20) We thank Professor Karl H. Overton of the University of Glasgow for providing us with generous samples of paniculides A as well as copies of the spectral data (i.e., ^1H and ^{13}C NMR).

(21) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983; Recipient of a National Institutes of Health (National Center Institute) Career Development Award, 1980–1985.

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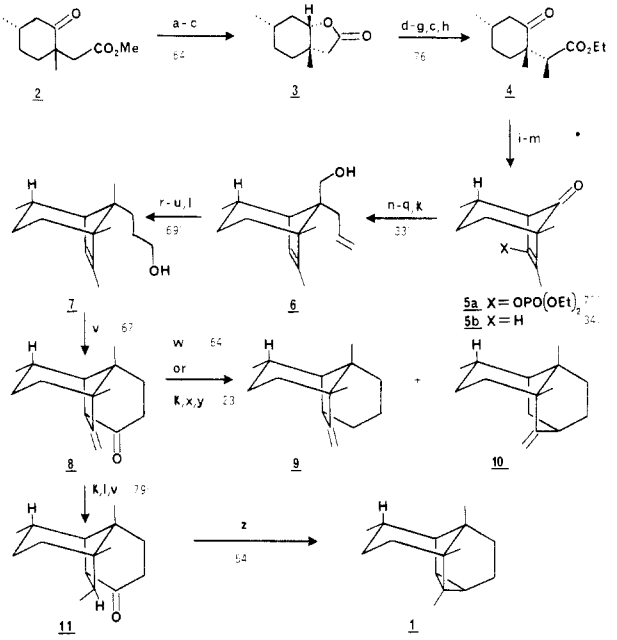
Received August 24, 1981

Synthesis of Seychellene and the Original Structure Reported for Cycloseychellene

Summary: A stereoselective total synthesis of the original structure **1** reported for cycloseychellene from 2,5-dimethylcyclohexanone is described. A synthesis of (±)-seychellene (**10**) is also presented.

Sir: Cycloseychellene, a tetracyclic sesquiterpene biogenetically related to seychellene (**10**), was isolated from *Pogostemon cablin* Benth. (Patchouli oil).[1,2] The structure of cycloseychellene was assigned as **1** on the basis of 220-MHz NMR data, as well as co-occurrence and equilibration [$Cu(OAc)_2$, HOAc, 90 °C] with seychellene (**10**).[2] A number of successful syntheses of seychellene (**10**) have been published;[3] however, no report on a synthesis of structure **1** has appeared in the chemical literature. The purpose of this communication is to present successful stereoselective syntheses of structure **1** and (±)-seychellene (**10**).

Scheme I[a]



[a] (a) KBH_4, MeOH, 0 °C; (b) NaOH, EtOH, H_2O; (c) H_3O^+; (d) LDA, THF; (e) CH_3I, (f) NaOH, *t*-BuOH, H_2O; (g) $RuCl_3$ 5 mol % and $NaIO_4$ added to f; (h) K_2CO_3, EtI, acetone; (i) 2.5 equiv of $NaN(SiMe_3)_2$, THF; (j) $ClPO(OEt)_2$, TMEDA; (k) $NaBH_4$, EtOH; (l) Li, $EtNH_2$, Et_2O, *t*-BuOH; (m) H_2CrO_4, acetone; (n) $Ph_3P{=}CHOMe$, Me_2SO; (o) $HClO_4$, H_2O, Et_2O; (p) Ph_3CK, DME; (q) $BrCH_2CH{=}CH_2$; (r) *n*-BuLi, THF, TMEDA; (s) $ClPO(NMe_2)_2$; (t) Sia_2BH, THF; (u) H_2O_2, OH^-; (v) $pyrH^+ClCrO_3^-$, CH_2Cl_2; (w) N_2H_4, KOH, DEG; (x) Ph_3P, NCS, THF; (y) $LiAlH_4$, THF; (z) *p*-TsNHNH$_2$, C_6H_6; NaH, DMF.

These syntheses begin with keto ester **2** which exists as a 70:30 mixture of *trans*-/*cis*-dimethyl diastereomers, respectively. Keto ester **2** is prepared from 2,5-dimethylcyclohexanone in 57% overall yield.[4] Reduction of keto ester **2** with KBH_4/CH_3OH at −15 °C followed by sequential treatment with NaOH/H_2O/EtOH and then 10% HCl for 20 h affords lactone **3** in 64% overall yield as a single diastereomer.[5] Alkylation of lactone **3**[6] by generating the enolate anion with LDA/THF and quenching with CH_3I affords the monomethylated lactone in 95%

(1) Wolff, G.; Ourisson, G., *Tetrahedron* **1969**, *25*, 4903.

(2) Terhune, S. J.; Hogg, J. W.; Lawrence, B. M., *Tetrahedron Lett.* **1973**, 4705.

(3) (a) Piers, E.; Britton, R. W.; de Waal, W. *J. Am. Chem. Soc.* **1971**, *93*, 5113. (b) Schmalzl, K. J.; Mirrington, R. N. *J. Org. Chem.* **1972**, *37*, 2877. (c) Fukamiya, N.; Kato, M.; Yoshikoshi, A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1843. (d) Frater, G.; *Helv. Chim. Acta* **1974**, *57*, 172. (e) Spitzner, D. *Tetrahedron Lett.* **1978**, 3349. (f) Jung, M. E.; McCombs, C. A. *J. Am. Chem. Soc.* **1978**, *100*, 5207. (g) Yamada, K.; Kyotani, Y.; Manabe, S.; Suzuki, M. *Tetrahedron* **1979**, *35*, 293. (h) Jung, M. E.; Pan, Y.-G. *Tetrahedron Lett.* **1980**, 3127.

(4) Welch, S. C.; Rao, A. S. C. P.; Gibbs, C. G.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077.

(5) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408. Diastereomeric *cis*-dimethyl-*trans*-hydroxy acid was isolated in 25% yield.

(6) Posner, G. H.; Loomis, G. L. *J. Chem. Soc., Chem. Commun.* **1972**, 892.

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