Synthesis of the Antileukemic Agent (\pm) -Steganone Using a Stereoconvergent Biaryl Coupling Reaction

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Abstract: The total synthesis of (\pm) -steganone (4) has been achieved in a stereoselective manner from piperonal. The cinnamate derivative 15 was oxidized by using Tl(OCOCF₃)₃ in TFA to give the biaryl 26 (81%). Reduction of 26 with LiAlH₄ gave 27, which was converted into the cyclopropylcarbinol 10 by the Simmons-Smith reaction. The same key substrate was also available by $Tl(OCOCF_3)_3$ oxidation of the cyclopropane adduct 9 (X = OMe) followed by reduction with LiAlH₄ to give 10. The former sequence is the preferred one. Solvolysis of 10 in AcOH accomplished ring expansion and the regio- and stereospecific introduction of the C-8 oxygen substituent to give 34. Hydroboration of 34 followed by base hydrolysis gave the diol 35, which establishes the correct relative stereochemistry between C-8 and the biaryl twist. Jones oxidation of 35 gave the known oxoacid 7, which was converted into (\pm) -steganone (4) by using the literature procedure.

In 1972, Kupchan¹ reported the isolation from Steganotaenia araliacea Hochst four dibenzocyclooctadiene lignans that exhibited significant activity in vivo against the P-388 leukemia in mice and in vitro against cells derived from human carcinoma of the nasopharynx (KB). These compounds, steganacin (1), steganangin (2), steganol (3), and steganone (4), belong to the unusual dibenzocyclooctadiene lignans² and, as such, immediately presented a very effective challenge for synthesis. This has been met by



reports of several syntheses that can be divided into three main classes. The first, and most efficient synthesis, by Raphael³ involves the construction of a 9-pyrrolidinophenanthrene by conrotatory cyclization of a stilbene derivative, followed by a two-carbon ring expansion. An important feature of this synthesis is that it allows for the direct regiospecific introduction of the benzylic oxygen functionality at C-8. The second very effective strategy was developed by Ziegler⁴ that involves the examination of modifications of the Ullmann reaction to give unsymmetrically substituted biaryls. The third, from a biosynthetic point of view, most interesting strategy has been reported by Kende⁵ and uses the so-called non-phenolic oxidation methodology,⁶ which resulted in the direct formation of the crucial biaryl bond concomitant with the eight-membered ring. Unfortunately, the attractiveness of the non-phenolic oxidation approach is curtailed by the apparent inability to carry out oxidative coupling in the presence of a benzylic oxygen substituent. Consequently, while this approach

(5) Kende, A. S.; Liebeskind, L. S. J. Am. Chem. Soc. 1976, 98, 267. Kende, A. S.; Liebeskind, L. S.; Kubiak, C.; Eisenberg, R. Ibid. 1976, 98, 6389.

(6) Kupchan, S. M.; Liepa, A. J. Kameswaran, V.; Bryan, R. F. J. Am. Chem. Soc. 1973, 95, 6861. Kupchan, S. M.; Kamwswaran, V.; Lynn, J. T.; Williams, D. K.; Liepa, A. J. Ibid. 1975, 97, 5622. Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K.; Kameswaran, V. J. Org. Chem. 1976, 41, 4047. Kupchan, S. M.; Khingra, O. P.; Kim, C.-K. Ibid. 1976, 41, 4049.

is direct, the C-8 oxygen substituent has to be introduced at a later stage by benzylic oxidation.⁷

An intriguing stereochemical problem occurred during the synthesis of steganone (4) and was first described in detail by Raphael.³ All the syntheses proceed through the oxoacid 6, which has the opposite biaryl twist relative to the ester group, required for the synthesis of steganone (4). Fortunately, the oxoacid 6



was equilibrated with its biaryl twist rotamer by heating in xylene (135 °C) to give a 1:1 mixture of 6 and 7. When the "wrong" oxoacid 6 is treated with aqueous KOH/CH₂O, followed by Jones oxidation (CH₂O treatment results in reduction), isosteganone (5) was formed (78%), which was thermally isomerized to steganone (4) through β elimination to 4a and recyclization to 4. It should be noted that epimerization at the carboxyl (or ester) group at C-6 is equivalent to a reversal of the biaryl twist. All the syntheses arrive at isosteganone (5) and thermally isomerize it into steganone 4. Fortunately, this transformation is almost quantitative because the driving force is provided by the movement of the C-8 carbonyl group in 5 ($\nu_{max} = 1710 \text{ cm}^{-1}$) into planarity with the piperonyl ring to give steganone 4 ($\nu_{max} = 1665 \text{ cm}^{-1}$).

Given the background outlined above, there are two problems that present themselves. First, how can non-phenolic biaryl coupling be carried out in the presence of a benzylic substituent, and second, is this strategy compatible with the direct formation of the requisite biaryl with the correct relative configuration with respect to the configuration at C-6?

Results

All our attempts to conduct non-phenolic oxidation using a range of reagents, VOF₃,⁶ FeCl₃,⁸ and Tl(OCOCF₃)₃,⁹ on the

⁽¹⁾ Kupchan, S. M; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. J.; Bryan, R. F., J. Am. Chem. Soc. 1973, 95, 1335.

<sup>N. J.; Diyan, K. F., J. Am. Chem. Soc. 1973, 95, 1335.
(2) For a recent general review on the synthesis of lignans and neolignans, see: Ward, R. S. Chem. Soc. Rev. 1982, 11, No, 2, 75.
(3) Becker, D.; Hughes, L. R.; Raphael, R. A. J. Chem. Soc., Perkin Trans. 1 1977, 1674. Becker, D.; Hughes, L. R.; Raphael, R. A. J. Chem. Soc., Chem. Commun. 1974, 430. Hughes, L. R.; Raphael, R. A. Tetrahedron Lett. 1976, 1543.</sup>

⁽⁴⁾ Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. J. Am. Chem. Soc. **1980**, 102, 790. Ziegler, F. E.; Fowler, K. W.; Kanfer, S. J. Ibid. **1976**, 98, 8282. Ziegler, F. E.; Fowler, K. W.; Sinha, N. D. Tetrahedron Lett. 1978, 2767.

⁽⁷⁾ The Kende synthesis of (\pm) -steganone reports extensive efforts to introduce the required benzylic oxygen atom at C-8 prior to oxidation to the biaryl system and states that attempted non-phenolic oxidation of substrates similar to 8 failed.

⁽⁸⁾ Ferric chloride supported on silica gel is a mild procedure for the oxidative coupling of phenols and phenol ethers: Jempty, T. C.; Millar, J. L.;

Mazur, Y. J. Org. Chem. 1980, 45, 749. (9) Taylor, E. C.; McKillop, A. Acc. Chem. Res. 1970, 3, 338; McKillop, A.; Fowler, J. S.; Zelesko, M. J.; Hunt, J. D.; Taulor, E. C.; McGillivray, G. *Tetrahedron Lett.* **1969**, 2423, 2427. For the oxidative dimerization of cinnamic acids using Tl(OCOCF₃)₃ see: Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A.; Tetrahedron Lett. **1978**, 3623. And: J. Org. Chem. **1981**, 46, 3078. McKillop, A.; Turrell, A. G.; Taylor, E. C. J. Org. Chem. **1977**, **42**, 764. This reference describes the oxidation of 1,3-bis(3,4-dimethoxyphenyl)propane to a biphenyl, bridged by three carbon atoms.

Scheme I



substrates 8 (X = H, OH; H, OAc; H, CN; H, SO₂Ph; OCH₂- CH_2O ; OCH_2CH_2S ; $OCH_2CH_2SO_2$; and H, SiMe₃) uniformly resulted in extensive decomposition with no clear evidence for the formation of the biaryl-coupled products. Consequently, a less direct approach was required that at least would enable the regiospecific introduction of an oxygen substituent at C-8. A plausible way to achieve this initial objective is to disguise both the eventual eight-membered ring and the oxygen functionality at C-8 in the form of a cyclopropane derivative. Controlled opening of the cyclopropane ring at an appropriate stage has the inherent potential to result in ring expansion and concomitant regio- and stereoselective placement of the C-8 oxygen atom. this strategy is outlined in Scheme I. The scheme requires the regiospecific synthesis of 9 ($X = CO_2R$), its oxidation to the biaryl 10 (X = CO_2R), and finally ring expansion, most probably via a cyclopropylcarbinol solvolysis reaction¹⁰ on 10 ($X = CH_2OH$) to give the dibenzocyclooctadiene 11.

3,4,5-Trimethoxybenzyl bromide was treated with t-BuO₂CCH₂P(O)(OEt)₂/NaH/THF to give the phosphonate 12, which was directly treated with NaH/piperonal to provide the α,β -unsaturated ester 14 as a mixture of E and Z isomers (2:1) in 38% yield. It was not necessary to separate these isomers, since



the treatment of α,β -unsaturated carbonyl compounds with dimethylsulfoxonium methylide is known to be nonstereospecific.¹¹ In the event, when 14 was treated with Me₂S⁺(O)CH₃I⁻/ NaH/THF, a single cyclopropane stereoisomer 16 was formed in 81.6% yield. Part of the chemical proof for the stereochemistry depicted for 16 was obtained in the following chemical correlations. (The choice, at this stage, of a *tert*-butyl ester was dictated by its ready removal under acidic conditions.)

The α,β -unsaturated nitrile **19** was converted into the cyclopropylnitrile **20**, using Me₂S⁺(O)CH₃I⁻/NaH/THF, and alkylated with 3,4,5-trimethoxybenzyl bromide/LiN-i-Pr₂/THF/-78 °C to give a single stereochemically homogeneous adduct 21. The alkylation of 20 has taken place with complete inversion, 12 and its assignment of stereochemistry ultimately rests upon the oxidative cyclization reactions described below. Treatment of 21 with alkaline hydrogen peroxide gave the amide 22, which was different (TLC, NMR, mp) from the amide 18 prepared by treating 16 with TFA to give the corresponding acid 18a and standard conversion (SOCl₂, followed by NH₃) into 18. Having established that the two routes to substrates suitable for biaryl oxidative cyclization give opposite stereochemistry about the cyclopropane, the only question is which is the correct cis arrangement of piperonyl to 3,4,5-trimethoxybenzyl? Obviously, only one of the cyclopropane stereoisomers is capable of undergoing oxidative coupling to a biaryl, thereby establishing the relative stereo-chemistry in a chemically conclusive fashion.

The *tert*-butyl ester **16** proved to be too labile to the acidic conditions normally used in non-phenolic oxidative cyclizations; consequently, we used the corresponding methyl ester **17**. Treatment of the *tert*-butyl ester **16** with *p*-TsOH·H₂O/toluene/reflux gave the corresponding carboxylic acid **16** (R = OH), which was exposed to diazomethane to provide the methyl ester **17** (92%). It should be noted that attempted cyclopropanation of **15** (see later) with Me₂S⁺(O)CH₃I⁻/NaH/THF resulted in 1,2-addition, whereas, the *tert*-butyl ester **14** gave the 1,4-adduct **16**.

Treatment of the ester 17 with $Tl(OCOCF_3)_3/TFA/O$ °C gave the biaryl 10 (X = CO₂Me) in 43% yield, as a single stereochemically homogeneous compound, assigned the relative configuration shown, based upon an alternative synthesis of the reduction product 10 (X = CH₂OH). The use of other one-electron oxidants such as VOF₃ or FeCl₃, silica gel, did not give any oxidative coupling but caused a Lewis acid-promoted intramolecular alkylation to give 23.¹³ The formation of the required



coupled product 10 (X = CO₂Me) allows the unambiguous assignment of the relative configurations of the various substituted cyclopropanes 16, 17, 18, 21, and 22 as shown. The benzylation of 20 must have taken place with complete inversion of configuration. The stereoconvergent cyclopropanation of the α,β -unsaturated ester 14 presumably implies that the intermediate sulfoxonium ion 14a is more stable than the conformer 14b where



there is a severe nonbonded interaction between the t-BuO⁻ group and the piperonyl ring. (A similar picture for 20, except that the cyclopropane ring is already formed, would predict inversion to give 21.)

The Tl(OCOCF₃)₃ biaryl coupling reaction was carried out in neat TFA for the following rationale: Treatment of 17 with Tl(OCOCF₃)₃/CH₂Cl₂/TFA(190 equiv) gave 10 (X = CO₂Me) in only 5% yield; the major product was the arylthallium adduct 24 (90%).¹⁴ When the arylthallium bis(trifluoroacetate) derivative 24 was worked up with KI/I₂, the aryliodide 25 was isolated in 76% yield.¹⁴ Photolysis of 25 in acetonitrile resulted in the slow

⁽¹⁰⁾ Cyclopropylcarbinyl cation rearrangements, see: Olah, G. A.; Liang, G. J. Am. Chem. Soc. 1976, 98, 7026. Friedrich, E. C.; Jassawalla, J. D. C. J. Org. Chem. 1979, 44, 4224. For a comprehensive review describing cyclopropane ring opening, see: Sarel, S.; Yovell, J.; Sarel-Imber, M. Angew. Chem., Int. Ed. Engl. 1968, 7, 577. Hanack, M.; Schneider, H.-J. Ibid. 1967, 6, 666. Solvolytic rearrangement route to ring-expanded steroids: Steinberg, N. G.; Rasmusson, G. H.; Reamer, R. A. J. Org. Chem. 1979, 44, 2294. Marshall, J. A.; Ellison, R. H. Ibid. 1975, 40, 2070. Hudrlik, P. F.; Rudnick, L. R.; Korzeniowski, S. H. J. Am. Chem. Soc. 1973, 95, 6848. Whalen, D. L.; Cooper, J. D. J. Org. Chem. 1978, 43, 432. For a general review of cyclopropane chemistry: see: Meijere, A. Angew. Chem., Int. Ed. Engl. 1979, 18, 809. Other examples of cyclopropanes in ring expansion reactions: Kohout, L.; Fajkos, J. Collect. Czech. Chem. Commun. 1974, 39, 1613. Bellamy, A. J.; Whitman, G. H. Tetrahedron 1968, 24, 247. Caine, D.; Gupton, J. T. J. Org. Chem. 1974, 39, 2654. Seebach, D.; Braun, M. Angew. Chem., Int. Ed. Engl. 1972, 11, 49. Reese, C. B.; Shaw, A. J. Am. Chem. Soc. 1970, 92, 2566. Parham, W. E.; Schweizer, E. E. Org. React., 1963, 13, 55. Amice, P.; Blanco, L.; Conia, J. M. Synthesis 1976, 196.

⁽¹¹⁾ For a description of the stereochemical consequences of dimethylsulfoxonium methylide additions to conjugated esters, see: Trost, B. M.; Melvin, L. S., Jr. "Sulfur Ylides, Emerging Synthetic Intermediates"; Academic Press: New York, 1975; pp 77-107.

⁽¹²⁾ Walborsky, H. M.; Motes, J. M. J. Am. Chem. Soc. 1970, 92, 2445.
Fox, M. A.; Chem, C.-C.; Campbell, K. A. J. Org. Chem. 1983, 48, 321.
(13) Murphy, W. S.; Wattanasin, S. J. Chem. Soc., Perkin Trans. 1 1981,

<sup>2920; 1982, 271, 1029.
(14)</sup> McKillop, A.; Hunt, J. D.; Zelesko, M. J.; Fower, J. S.; Taylor, E. C.; McGillivray, G. M.; Kienzle, F. J. Am. Chem. Soc. 1971, 93, 4841.



conversion of 25 into the biaryl 10 (X = CO₂Me) in low yield. Treatment of 24 with $PdCl_2/AcOH/AcONa/90$ °C did not give any biaryl 10 (X = CO₂Me).¹⁵

Since it is known that arylthallation is a reversible electrophilic substitution reaction, an obvious recourse was to conduct the $Tl(OCOCF_3)_3$ oxidation in strongly acidic media in order to protonate 24 reversibly, and subsequent irreversible oxidation of 17 to 10 (X = CO₂Me) should convert 24 into 10 (X = CO₂Me). In this way, we arrived at the conditions (neat TFA) that gave the required biaryl 10 (X = CO₂Me) in 43% yield.

It should be noted that at this stage, we did not know the relative configuration of the biaryl twist in $10 (X = CO_2Me)$ with respect to the cyclopropane, other than 10 (X = COMe), was a single compound.

During the $Tl(OCOCF_3)_3$ oxidation of 17 to 10 (X = CO₂Me), we isolated a small quantity (ca. 2%) of a highly fluorescent compound assigned the structure 26. Since the R_f 's of 14 and 16 are virtually identical, apparently a small amount of unreacted 14 was converted into the methyl ester 15 and exposed to the $Tl(OCOCF_3)_3$ procedure to give the allocolchicine derivative 26.¹⁷ To test that this was the case, the phosphonate 13 was treated with NaH/DME/piperonal/20 °C to give the (E)- α , β -unsaturated ester 15 (91.5%) (containing less than 5% of the Z isomer). When the solution of 15 in TFA at -18 °C was treated with Tl(OCO- CF_{3} (1.15 equiv) the biaryl 26 was isolated after chromatography in 81% yield. This yield is approximately twice that normally associated with non-phenolic oxidations in the steganone lignan area.^{5,6} To correlate 26 with the biaryl 10 (X = CO_2Me), 26 was reduced with LiAlH₄ to give the allylic alcohol 27 (71%) and exposed to the Simmons-Smith cyclopropanation conditions $Zn/Cu/CH_2I_2/Et_2O$ to provide the cyclopropylcarbinol 10 (X = CH₂OH) (74%). The stereochemistry depicted for 10 (X =



CH₂OH) is based upon cyclopropanation from the least-hindered face of the allylic double bond opposite the trimethoxybenzene ring in 27. Reduction of 10 (X = CO₂Me) with LiAlH₄ gave 10 (X = CH₂OH) identical with the material prepared by the above route. Consequently, we can assign 10 (X = CO₂Me) the stereochemistry shown. The spirodiene intermediate 9a accounts for the stereochemical result and is considerably less hindered than the cyclopropane epimer.

The preferred route to 10 (X = CH₂OH) is via the cinnamate 15 and allocolchicine derivative 26. It was of some interest to examine whether or not other simple cinnamate derivatives could be oxidized in a similar fashion. In particular, is it possible to produce an eight-membered ring directly? The dianion of the Stobbe condensation product 28 was treated with 3,4,5-trimethoxybenzyl bromide to give 29. Exposure of 29 to Tl(OCOCF₃)₃ under a number of conditions did not give any of the desired eight-membered ring adduct 30; instead, only arylthallation resulted. Similarly, the stilbene derivative 31 did not give the corresponding phenanthrene compound on treatment with Tl(O-COCF₃)₃.



It was established that the geometry of the double bond in 15 does not drastically affect the oxidation to 10 (X = CO_2Me). In a separate series of experiments, pure (E)-15 was converted into 10 (X = CO_2Me) (70%) by using the Tl(OCOCF₃)₃ procedure, and pure (Z)-15 was also converted into 10 (X = CO_2Me) (28%).



The stereoconvergent nature of the oxidative coupling reaction was shown to be the result of acid-catalyzed (TFA) equilibration of E and Z isomers, rather than oxidation of the cinnamate 15 to the radical cation 15a.

In order to complete the synthesis the seven-membered ring, adduct 10 (X = CO_2Me) must be expanded to an eight-membered ring. Treatment of 10 (X = CO_2Me) with a variety of electrophiles did not initiate ring expansion, whereas treatment of 10 (X = CH₂OH) with AcOH/AcONa/HClO₄/45 °C for 3h gave 32 (97%) as a single stereoisomer.^{10'} It is not clear whether or not inversion or retention of configuration at C-8 has taken place. While an extensively delocalized carbonium such as 32a predicts retention of configuration, since acetate anion would be expected to quench 32a from the underside opposite the trimethoxyaryl ring to give 11, it creates substantial strain in the intermediate ion 32a. A more plausible alternative is a concerted reaction that results in inversion at C-8 to give 32. It should also be noted that the stereochemistry at C-8 is removed in the process of transforming the oxoacid 7 into steganone 4.3 The correct relative configuration between C-6 and the biaryl twist was established by hydroboration $BH_3/THF/0$ °C followed by $H_2O_2/NaOH$ and hydrolysis $K_2CO_3/H_2O/MeOH$ to give the diol 33 as a single stereoisomer. To unequivocally establish the stereochemistry of C-6 with respect to the biaryl twist, 35 was oxidized by using Jones reagent at 20 °C to give the known oxoacid 7 (80%), which on treatment with diazomethane gave the ester 7a, mp 132.5–136 °C (from MeOH) (lit.^{3,5} mp 133–134 °C). The oxoacid 7 was converted into (±)-steganone (4) by using standard conditions (5% KOH/37% CH₂O, followed by Jones oxidation) and was identical with an authentic sample kindly supplied by Dr. A. T. Sneden from the collection of the late Prof. S. M. Kupchan.

The synthesis of the oxoacid 7 produces the correct relative configuration between the C-6 substituent and the biaryl twist, whereas the other syntheses¹⁸ produce the isomeric oxoacid 6 and

⁽¹⁵⁾ Uemura, S.; Ikeda, Y.; Ichikawa, K. Chem. Commun. 1971, 390. (16) Roberts, R. M. G. Tetrahedron 1980, 36, 3281. See also ref 9.

⁽¹⁰⁾ Koleris, K. M. G. *Tetrahearon* 1980, 50, 3281. See also fel 9. (17) Santa<acyvy, F. *Helv. Chim. Acta* 1948, 31, 821. Fernholz, H. *Ann.* 1950, 568, 63. Ford, W. T.; Mewcomb, M. J. Am. Chem. Soc. 1973, 95, 6277.

⁽¹⁸⁾ For other syntheses of steganone and isosteganone, see: Krow, G. R.; Damodaran, K. M.; Michener, E.; Wolf, R.; Guare, J. J. Org. Chem. 1978, 43, 3950. Damon, R. E.; Schlessinger, R. H.; Blount, J. F. Ibid. 1976, 41, 3773. Brown, E.; Dhal, R.; Robin, J.-P. Tetrahedron 1983, 39, 2787. Tomioka, K.; Mizuguchi, H.; Koga, K. Tetrahedron Lett. 1979, 1409. Tomioka, K.; Ishiguro, T.; Koga, K. Ibid. 1980, 2973. Merić, M.; Ben-David, Y.; Ghera, E. Ibid. 1981, 5091. Tomioka, K.; Ishiguro, T.; Koga, K. J. Chem. Soc. Chem. Commun. 1979, 652. Robin, J.-P.; Gringpore, O.; Brown, E. Tetrahedron Lett. 1980, 2709. All structures are represented by a single enantiomeric form to depict racemic compounds. The correct absolute configuration of 4 was correctly determined by Koga and is antipodal to the enantiomers drawn in this paper.

convert it into isosteganone 5, which thermally isomerizes to steganone (4). The synthesis of the oxoacid 7 from piperonal proceeds in nine steps in an overall yield of 24%.

Experimental Section

(E)- and (Z)-tert-Butyl 2-[3,4-(Methylenedioxy)benzylidene)-3-(3,4,5-trimethoxyphenyl)propanoate (14). tert-Butyl diethylphosphonoacetate (1.00 g, 4 mmol) in dry glyme (15 mL) at 0 °C was treated with NaH (100 mg, 98%), followed by 3,4,5-trimethoxybenzyl bromide (1.04 g, 4 mmol) in glyme (10 mL). After 1 h at 25 °C, additional NaH (170 mg) was added, the mixture cooled at 0 °C, and piperonal (600 mg, 4 mmol) in glyme (10 mL) added. The above solution was quenched after 0.5 h with 5% aqueous NaHSO3 (100 mL) and extracted with EtOAc $(4 \times 30 \text{ mL})$. The dried (Na₂SO₄) extract was evaporated in vacuo, and the reside was purified by flash chromatography over silica gel eluting with EtOAc/petrol (9:1) to give 14 (650 mg, 38% based on piperonal): mp 93-96 °C (E isomer crystallized from light petroleum); IR (thin film) 1700, 1585, 1240, 1155, and 1125 cm⁻¹; NMR δ 7.7 (1 H, s), 6.7-6.9 (3 H, m), 6.4 (2 H, d), 5.9 (2 H, s), 3.8 (9 H, 3s), 3.8 (2 H, s), 1.4 (9 H, s). Anal. Calcd for C24H28O7: C, 67.41; H, 6.38. Found: C, 67.27; H, 6.59%.

cis-tert-Butyl 1-(3,4,5-Trimethoxybenzyl)-2-[3,4-(methylenedioxy)phenyl]cyclopropanecarboxylate (16). Dimethylsulfoxonium methylide (3.0 equiv generated from trimethylsulfoxonium iodide and NaH) in dry Me₂SO (20 mLe) at 20 °C was treated with the ester 14 (3.4 g) in Me₂SO (10 mL). The mixture was stirred for 2 h at 20 °C and then 15 h at 60 °C. The solution was concentrated under vacuum to ca. 10 mL and quenched with saturated aqueous NH4Cl solution. The product was extracted with EtOAc (5×20 mL), and the extracts were washed with brine and dried (Na₂SO₄). Evaporation of the solvent in vacuo and flash chromatography of the residue over silica gel gave 16 (2.72 g, 81.6%): mp 103-105 °C (from ether/petrol); IR 1705, 1590, 1500, 1485, 1230, 1210, 1120 cm⁻¹; NMR δ 6.7 (3 H, br s), 6.3 (2 H, br s), 5.9 (2 H, s), 2.7 (1 H, t), 2.5 (2 H, ABq, $\Delta v = 84$, J = 15 Hz), 1.7 (1 H, d of d), 1.1 (1 H, d of d); $MS m/e C_{25}H_{30}O_7 442 M - CH) 429 (12), 428 (45), 373$ (22), 372 (100), 371 (21), 353 (17), 311 (20). No parent ion was observed.

cis-Methyl 1-(3,4,5-Trimethoxybenzyl)-2-[3,4-(methylenedioxy)phenyl]cyclopropanecarboxylate (17). To a solution of the tert-butyl ester 16 (1.1 g) in toluene (20 mL) was added p-TsOH (5 mg) and the mixture heated at reflux for 10 h. The solvent was evaporated and the residue purified by flash chromatography, eluting with 80% CHCl₃/20% petrol to give the acid 18a (R = OH) (720 mg, 76%): mp 168-169 °C (from benzene/petrol); IR 3600-2500 (br, OH), 1690, 1590, 1490; NMR δ 10.2 (1 H, br), 6.85 (3 H, m), 6.5 (2 H, s), 3.95 (9 H, s), 2.97 (1 H, t, J = 8 Hz), 2.6 (2 H, ABq, J = 15 Hz, $\Delta \nu = 250$), 1.95 (1 H, d of d, J = 5, 12 Hz), 1.45 (1 H, t, J = 5 Hz), MS, m/e calcd. for $C_{21}H_{22}O_7$ 386 (46), 302 (11), 301 (56), 251 (11), 181 (100). A solution of the above acid 18a (R = OH) (310 mg, 0.81 mmol) in CH₂Cl₂ (10 mL) at 0 °C was treated with excess diazomethane to give 17 (295 mg 92%); IR 1709, 1585, 1482, 1425; NMR & 6.8 (3 H, m), 6.4 (2 H, s), 6.0 (2 H, s), 3.85 (9 H, s), 3.75 (3 H, s), 2.85 (1 H, t, J = 8 Hz) 2.6 (2 H, ABq, J = 12Hz, $\Delta \nu = 240$), 1.85 (1 H, d of d, J = 5, 10 Hz), 1.3 (1 H, t, J = 8 Hz); MS, m/e calcd for C₂₂H₂₄O₇ 400 (39), 386 (21), 326 (10), 301 (36), 181 (100)

Methyl 2,3-(Methylenedioxy)-8,9,10-trimethoxydibenzo[a,c]cyclopropa[e]cycloheptane- $5\alpha\beta(4b\beta H)$ -carboxylate (10) (X = CO₂Me). To a solution of the cyclopropyl ester 17 (350 mg) in dry TFA (8 mL) at -18 °C under argon was added thallium tris (trifluoroacetate) (550 mg) in one portion with rapid stirring. The dark green mixture was left between -15 and -18 °C for 25 min and then quenched with water (40 mL). The solution was extracted with EtOAc (4×20 mL), dried (Na₂SO₄), and evaporated in vacuo to give a residue that was purified by flash chromatography over silica gel, eluting with 10% EtOAc/90% petrol to give 10 (R = CO₂Me) (150 mg, 43%): mp 136-138 °C (from EtOAc/hexane); IR (CHCl₃) 1710, 1600, 1465, 1130, 1100, and 1030 cm⁻¹; NMR (360 MHz) δ 0.97 (1 H, dd, J = 4.2, 3.3 Hz), 1.48 (1 H, dd, J = 4, 9.4 Hz), 2.60 (1 H, dd, J = 5.7, 9.3 Hz), 2.75 (2 H, ABq, J= 13.7 Hz, $\Delta \nu_{AB}$ = 444), 3.62 (3 H, s), 3.63 (3 H, s), 3.90 (6 H, s), 5.96 $(2 \text{ H}, \text{ABq}, J = 1.3 \text{ Hz}, \Delta \nu_{\text{AB}} = 8), 6.78 (1 \text{ H}, \text{s}), 6.91 (1 \text{ H}, \text{s}), 6.93 (1 \text{ H}, \text{s}))$ H, s); MS, m/e calcd for $C_{22}H_{22}O_7$ 398.136, found 398.136.

When the TFAA oxidation was carried out in CCl₄/TFA (9:1) and the reaction mixture worked up with KI (1 g)/I₂ (200 mg)/H₂O (10 mL), the iodide **25** (40 mg, from 40 mg of **17**, representing a 76% yield) was isolated.

A solution of the iodide 25 (10 mg) in acetonitrile (8 mL) was irradiated in a Pyrex tube using a 450-W high-pressure mercury lamp. Slow conversion into 10 ($R = CO_2Me$) was observed.

Treatment of 17 with VOF₃ or FeCl₃ gave the tetralin derivative 23: NMR δ 6.6–6.8 (3 H, m), 6.4 (1 H, s), 5.9 (2 H, s), 4.2 (1 H, t), 3.85–4.9

(9 H, 3s), 3.2 (3 H, s), 3.09 (2 H, ABq, J = 16 Hz, $\Delta \nu = 209$), 3.05 (1 H, 5s), 2.25 (1 H, m), 2.05 (1 H, t).

(E)-Methyl 2-[3,4-(Methylenedioxy)benzylidene]-3-(3,4,5-trimethoxyphenyl)propanoate (15). To a solution of the phosphonate 13 (100 mg, 0.256 mmol) in DME (5 mL was added NaH (13 mg) at 0 °C followed by piperonal (38 mg). After 12 h at 20 °C, the mixture was quenched with saturated aqueous NH₄Cl solution, extracted with CH₂Cl₂ (3 × 10 mL), dried (MgSO₄), and evaporated to give the crude product, which chromatographed over silica gel, eluting with 20% EtOAc/petrol to give 15 (88 mg, 91.5%) as thick oil: IR (thin film) 1700, 1585, 1490, 1230, and 1120 cm⁻¹; NMR (90 MHz) δ 7.8 (1 H, s), 6.7–6.9 (3 H, m), 6.3–6.4 (2 H, m), 5.9 (2 H, s), 3.7–3.8 (9 H, 3s), 3.6 (2 H, s). Anal. Calcd for C₂₁H₂₂O₇: C, 65.28; H, 5.74. Found: C, 65.41; H, 5.84.

Methyl 2,3- (Methylenedioxy)-9,10,11-trimethoxydibenzo[a,c]cycloheptene-6-carboxylate (26). To a solution of 15 (3.03 g) in TFA (39.2 mL) at -18 °C was added thallium tris(trifluoroacetate) (4.9 g) in one portion. After 0.5 h at -18 °C, the mixture was quenched with ice water (100 mL) and extracted with EtOAc (200 mL). The extract was washed with brine (2 × 100 mL), dried (MgSO₄), and evaporated and toluene added. Evaporation in vacuo and chromatography of the residue over silica gel eluting with 10% EtOAc/petrol gave 26 (2.48 g 81%), as a colorless foam: IR (CHCl₃) 1695, 1590, 1480, 1400, 1270, 1100, and 1033 cm⁻¹; UV (EtOH) max 203, 252 nm (ϵ 3.74 × 10⁴, 3.42 × 10⁴); NMR (360 MHz) δ 7.49 (1 H, br s), 7.32 (1 H, s), 6.85 (1 H, s), 6.65 (1 H, s), 6.04 (2 H, ABq, J = 1 Hz, $\Delta \nu_{AB} = 21$), 3.89 (3 H, s), 3.87 (3 H, s), 3.80 (3 H, s), 3.23 (2 H, ABq, J = 13 Hz, $\Delta \nu_{AB} = 400$), 3.49 (3 H, s), 4.59.

2,3-(Methylenedioxy)-9,10,11-trimethoxydibenzo[*a*,*c***]cycloheptenyl-6-carbinol (27).** To the ester **26** (1.857 g, 4.83 mmol) in THF (10 mL) at -78 °C was added LiAlH₄ (183 mg) and the mixture warmed to 0 °C. Workup in the standard manner gave **27** (1.22 g after recrystallization from benzene, 71%): mp 152-153 °C (from benzene); IR (CHCl₃) 3600, 2980, 2920, 2880, 2820, 1590, 1490, 1470, 1400, 1130, 1090, and 1030 cm⁻¹; NMR (360 MHz) δ 6.75 (1 H, s), 6.55 (1 H, s), 6.34 (1 H, br s), 5.9 (2 H, dAu = 23), 4.29 (2 H, br s), 3.87 (3 H, s), 3.85 (3 H, s), 3.49 (3 H, s), 2.90 (2 H, ABq, J = 13 Hz, $\Delta \nu$ = 98), 1.78 (1 H, br s exchanged by D₂O). Anal. Calcd for C₂₀H₂₀O₆: C, 67.40; H, 5.66. Found: C, 67.47; H, 5.41.

2,3-(Methylenedioxy)-8,9,10-trimethoxydibenzo[a,c]cyclopropa[e]cycloheptyl-5a β (4b β H)-carbinol (10) (X = CH₂OH). To a freshly prepared Zu(Cu) couple (552 mg, 2.75 equiv) in Et₂O (3 mL) was added I_2 (5 mg), the mixture heated at reflux for 1 min, and CH_2I_2 (538 mL 2.15 eq) added over 3 min. After heating at reflux for 45 min, a solution of 27 (1.1 g) in toluene (7 mL) was added and the mixture refluxed for 1 h. The cooled mixture was quenched with water (6 mL) and extracted with CH₂Cl₂ (20 mL). The dried (MgSO₄) extract was evaporated in vacuo and the residue chromatographed over silica gel, eluting with 1:1 EtOAc/hexane to give 10 (X = CH₂OH) (847 mg, 74%): mp 153-154 °C (from Et₂O/petrol); IR (CHCl₃) 3600, 3450, 1590, 1480, 1450, 1400, and 1320 cm⁻¹; NMR & 6.93 (1 H, s), 6.89 (1 H, s), 6.65 (1 H, s), 5.95 (2 H, d with each peak finely split, $\Delta v = 9$), 3.90 (6 H, s), 3.72 (1 H, lower half of an ABq centered at 2.92, $\Delta \nu = 579$, J = 11 Hz), 3.63 (3 H, s), 2.95 (1 H, AQb, $\Delta v = 29$, J = 13.5 Hz), 2.12 (1 H, upper half of an ABq centered at 2.92, $\Delta v = 579$, J = 11 Hz), 1.67 (1 H, d of d, $d_1 = 4, d_2 = 9$, 1.45 (OH, br), 0.95 (1 H, d of d, d = 4.4, d_2 = 9), 0.66 (1 H, t with each peak split further, J = 4.3 Hz); MS, m/e calcd for C21H22O6 370.142, found 370.141.

Treatment of the ester 10 (X = CO₂Me) (75 mg) in ether (5 mL) with LiAlH₄ (50 mg) in ether (2 mL) at 0 °C for 10 min gave the carbinol 10 (X = CH₂OH) (35 mg, 75%), identical in all respects with the material made through the Simmons-Smith cyclopropanation route.

5,7,8-Trihydro-1,2,3-trimethoxy-10,11-(methylenedioxy)-6methylene-8\beta-acetoxydibenzo[a,c]cyclooctene (32). The cyclopropylcarbinol 10 (X = CH₂OH) (239 mg) in AcOH (3 mL) containing Na-OAc (100 mg) and $HClO_4$ (10 drops) was heated at 45 °C for 3 h, poured onto powdered Na₂CO₃, and lyophilized to remove AcOH. The residue was treated with water (10 mL), CHCl₃ (30 mL), and solid Na₂CO₃ until the aqueous phase was basic. The aqueous phase was further extracted with CHCl₃, and the combined extracts were dried (MsSO₄) and evaporated in vacuo. The residue was chromatographed over silica gel eluting with 20% EtOAc/petrol to give 32 (99 mg, 37%) and the unrearranged acetate derived from 10 (X = CH_2OH), namely 10 (X = CH₂OAc) (159 mg, 60%). The yield of 32 is 97% based upon the recovery of 10 (X = CH_2OAc), which can be converted into 32 by the above solvolysis conditions. It should be noted that prolonged solvolysis decreases the yield of 32. The compound 32 has mp 148-149.5 °C: IR (CHCl₃) 1730, 1590, and 1480 cm⁻¹; NMR δ 7.0 (1 H, s), 6.75 (1 H, s), 6.6 (1 H, s), 6.0 (2 H, d, J = 6 Hz), 5.3 (1 H, m), 5.0 (1 H, m)br s), 4.82 (1 H, br s), 3.9 (6 H, 2s), 3.8 (3 H, s), 3.15 (1 H, lower half

of ABq, J = 12 Hz), 2.55–2.75 (3 H, br m), 2.0 (3 H, s). Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 67.11; H, 5.99.

5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-(methylenedioxy)-8ßhydroxydibenzo[a,c]cyclooctenyl-6 β -carbinol (33). To a solution of 32 (252 mg, 0.61 mmol) in THF (1.2 mL) at 0 °C was added a solution of BH₃·THF (3.12 mL, 0.98 M) and the mixture warmed to 20 °C. After 0.5 h, the solution was cooled to 0 °C and 3 N NaOH (4 mL) added, followed by 30% H₂O₂ (4 mL), and stirred at 20 °C for 20 min, and saturated with solid K_2CO_3 . The layers were separated, and the aqueous layer was extracted with EtOAc (3 \times 20 mL, dried (MgSO₄), and evaporated in vacuo. The residue was dissolved in MeOH (3 mL) and water (3 mL), and K₂CO₃ was (400 mg) added. After 12 h at 20 °C, the mixture was diluted with water (10 mL) and extracted with EtOAc (10 mL) and CH_2Cl_2 (2 × 10 mL), dried (MgSO₄), and evaporated in vacuo. The residue was stirred with powdered K₂CO₂ (400 mg) in 1:1 MeOH-H₂O (6 mL) for 12 h at room temperature, diluted with water, extracted with ethyl acetate (10 mL) and methylene chloride (20 mL), and dried (MgSO₄) and the solvent evaporated to give 33 (219 mg, 92.4%). Recrystallization gave pure 33, mp 191-192 °C (from benzene/chloroform), 190 mg, 80%: IR (CHCl₃) 3600, 1590, 1486, 1140, 1100, and 1035 cm⁻¹; NMR (360 MHz) 8 7.16 (1 H, s), 7.08 (1 H, s), 6.6 (1 H, s), 6.55 (1 H, s), 5.90 (2 H, d, J = 10 Hz), 4.3 (1 H, d, J =10 Hz), 3.8 (6 H, s), 3.6 (3 H, s), 2.8 (1 H, m), 2.3 (1 H, d, J = 13 Hz), 2.1 (1 H, br m), 2.0 (1 H, d, J = 13 Hz), 1.8 (2 H, br m). Anal. Calcd for C₂₁H₂₄O₇: C, 64.94; H, 6.23. Found: C, 64.99; H, 6.27.

Methyl 5,6,7,8-Tetrahydro-1,2,3-trimethoxy-10,11-(methylenedioxy)-8-oxodibenzo[a,c]cyclooctene-6 β -carboxylate (7a). To a solution of the diol 33 (190 mg, 0.49 mmol) in acetone (10 mL) was added freshly prepared Jones reagent (0.35 mL of a solution prepared from 1.34 g of $CrO_3/1.2$ of mL 6 N H₂SO₄ in 10 mL of H₂O). After 2.5 h at 20 °C, the mixture was quenched with MeOH and worked up in the standard manner to give the oxoacid 7 (157 mg, 80%): NMR (360 l Hz) δ 7.68 (1 H, s), 6.67 (1 H, s), 6.55 (1 H, s), 6.07 (2 H, d, J = 9 Hz), 3.92 (3 H, s), 3.83 (3 H, s), 3.58 (3 H, s), 3.16 (1 H, ABq centered at 2.98, J= 13.7 Hz, $\Delta \nu_{AB}$ = 134), 3.05 (1 H, br m), 2.85 (1 H, t, J = 7 Hz), 2.8 (1 H, dd, J = 14, 1 Hz), 2.62 (1 H, t, J = 13 Hz).

To a solution of the oxoacid 7 (157 mg) in ether (10 mL) was added excess ethereal diazomethane at 0 °C. Evaporation and chromatography over silica gel, eluting with petrol-EtOAc (4:1), gave the oxo ester 7a (115 mg, 70%): mp 132.5-136 °C (from MeOH) [lit.³ 133-134 °C]; NMR δ 7.67 (1 H, s), 6.66 (1 H, s), 6.45 (1 H, s), 6.05 (2 H, d, J = 11 Hz), 3.91 (3 H, s), 3.85 (3 H, s), 3.71 (3 H, s), 3.56 (3 H, s), 3.13 (1 H, lower half of ABq, J = 14 Hz), 3.0 (1 H, m), 2.8 (2 H, m), 2.6 (1 H, t, J = 13 Hz).

(\pm)-Steganone (4). Oxoacid 7 (46 mg) was stirred with 5% KOH (1 mL) and 37% CH₂O (0.2 mL) for 2 h. The mixture was acidified with 3 N HCl, extracted with CHCl₃ (3 × 5 mL), dried (MgSO₄), and the solvent was removed under reduced pressure. The residue was taken up in acetone (3 mL) and at 0 °C; Jones reagent was added until the orange persisted. Excess Jones reagent was destroyed with MeOH. Water was added, and the mixture was extracted with CHCl₃ (3 × 5 mL). The combined chloroform extracts were washed with 1 N NaOH. The CHCl₃ solution was dried (MgSO₄) and the solvent removed to afford (\pm)-steganone (4) (8 mg 17%). Recrystallization from CH₂Cl₂-EtOH provided material were indentical, with the exception of rotation, with a sample of natural (\pm)-steganone.

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Registry No. (\pm)-4, 58800-45-6; (\pm)-7, 65310-09-0; (\pm)-7a, 65310-11-4; (\pm)-10 (X = CO₂Me), 97253-43-5; (\pm)-10 (X = CH₂OH), 95238-10-1; (\pm)-10 (X = CH₂OAc), 97253-47-9; (\pm)-13, 97253-46-8; (*E*)-14, 97253-38-8; (*Z*)-14, 97253-39-9; (*E*)-15, 95238-06-5; (*Z*)-15, 95238-07-6; (\pm)-16, 97253-40-2; (\pm)-17, 97253-42-4; (\pm)-18, 97253-50-4; (\pm)-18a, 97253-41-3; 19, 61833-23-6; (\pm)-20, 97253-48-0; (\pm)-21, 97253-49-1; (\pm)-22, 97277-60-6; 23, 97253-45-7; (\pm)-24, 97293-66-8; (\pm)-25, 97253-44-6; (\pm)-26, 95238-08-7; (\pm)-27, 95238-09-8; (\pm)-32, 95238-11-2; (\pm)-33, 95238-12-3; *tert*-butyl diethylphosphonoacetate, 27784-76-5; 3,4,5-trimethoxybenzyl bromide, 21852-50-6; piperonal, 120-57-0; dimethylsulfoxonium methylide, 5367-24-8.

Supplementary Material Available: Experimental details for **19–22** (2 pages). Ordering information is given on any current masthead page.