Total Synthesis of 11-Deoxydaunomycinone by a New Annulation Process

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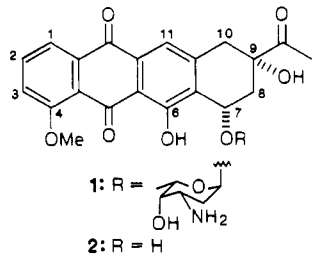
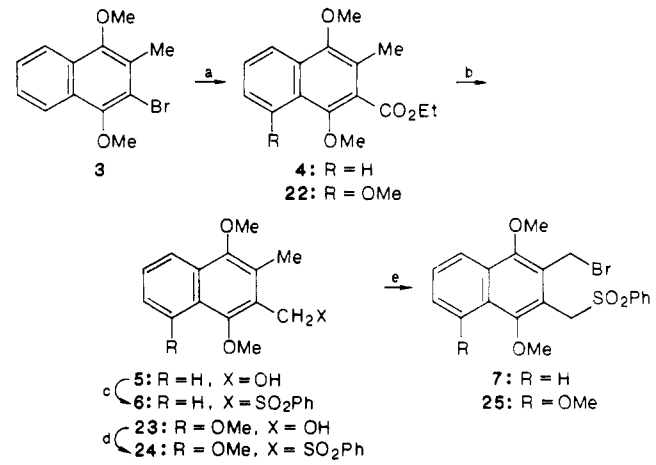
The one-pot regioselective formation of the tetracyclic product **26** by the base-induced addition of 2-(bromomethyl)-3-[(phenylsulfonyl)methyl]-1,4,5-trimethoxynaphthalene (**25**) to 4-(benzyloxy)cyclohexanone (**11**) serves as the key process for a new synthesis of 11-deoxydaunomycinone. Further steps involve a desulfonylation–dehydration sequence followed by the transformation to diols **28a,b** and **29a,b**, which, after separation, were both converted via a Swern oxidation into the precursor of 11-deoxyanthracyclinones (**38**) in 30% overall yield from the bicyclic **25**. The yields of conversion of ketone **38** into 7,11-dideoxydaunomycinone (**40**) were improved by the utilization of an ethynyl cerium(III) reagent, despite its unexpected addition to the quinone carbonyl, which was, however, reversible during hydration. In the 4-demethoxy series, the established precursor **21** was obtained via the cleavage of the dioxolane ring in **17** induced during oxidation with the CrO_3–DMP complex, to give the enol ether **18**.

The antitumor activity of certain anthracyclines, like daunomycin and adriamycin, led to a widespread interest in the synthesis of these compounds and resulted in a great variety of conceptually innovative solutions which are concerned mainly with the synthesis of the aglycon part of the antibiotic molecule.[1,2] The search for more active analogues led to the isolation of 11-deoxyanthracyclines with significant antitumor activity and a diminished cardiotoxicity.[3] The syntheses of the aglycon fragment **2** of 11-deoxydaunomycin (**1**),[4] like the syntheses of other anthracyclinones, were classified into a few categories, depending on the methodology utilized for the construction of the tetracyclic framework.[1] Of these synthetic concepts, various Diels–Alder reactions and Michael-induced ring-closure reactions were, until now, the sole processes for ensuring the formation of tetracyclic intermediates by one-vessel regioselective coupling of two building blocks, both C–C bonds being formed under identical reaction conditions.[5] In the present paper, we report an effective synthesis of 11-deoxydaunomycinone (**2**), which fulfills, as well, the above-mentioned conditions by utilizing, however, a different anionic process.

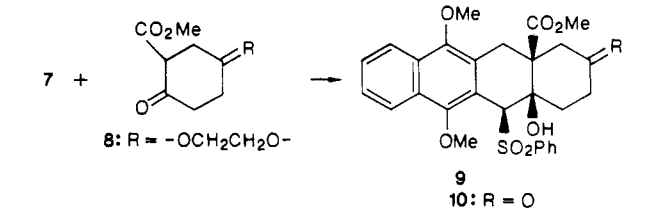


Scheme I[a]



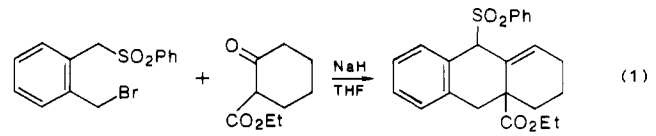
[a] (a) BuLi, $ClCO_2Et$; (b) $LiAlH_4$; (C) NBS, Me_2S; $PhSO_2Na$; (d) PBr_3; $PhSO_2Na$; (e) NBS, $h\nu$.

Scheme II



Results and Discussion

Initial attempts for the development of an approach for the synthesis of **2** were based on our previous findings that an *o*-xylene derivative bifunctionalized at the benzylic positions with Br and SO_2Ph groups can react with 2-oxocyclohexanecarboxylate in the presence of base to afford a tricyclic product (eq 1).[6] Hence, we undertook the



(1)

(1) For a recent review, see: Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790.

(2) Tetrahedron Symposia-in-Print 17, *Tetrahedron* **1984**, *40*, 4539–4793.

(3) Arcamone, F.; Cassinelli, G.; Di Matteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462.

(4) For total or formal total syntheses of **2**, see: (a) Gesson, J. P.; Jacquesy, J. C.; Mondon, M. *Tetrahedron Lett.* **1980**, *21*, 3351. (b) Gesson, J. P.; Mondon, M. *J. Chem. Soc., Chem. Commun.* **1982**, 421. (c) Bauman, J. C.; Barber, R. B.; Gless, R. D.; Rapoport, H. *Tetrahedron Lett.* **1980**, *21*, 4777. (d) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysoglu, T. *Tetrahedron Lett.* **1981**, *22*, 3711. (e) Yadav, J.; Corey, P.; Hsu, C.-T.; Perlman, K.; Sih, C. J. *Tetrahedron Lett.* **1981**, *22*, 811. (f) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (g) Rao, A. V. R.; Deshpande, V. H.; Reddy, N. L. *Tetrahedron Lett.* **1982**, *23*, 775. (h) Rao, A. V. R.; Reddy, N. L.; Mehendal, A. R. *J. Chem. Soc., Chem. Commun.* **1983**, 564. (i) Kende, A. S.; Boettger, S. D. *J. Org. Chem.* **1981**, *46*, 2799. (j) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688. (k) Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, *48*, 1328. (l) Vedejs, E.; Miller, W. H.; Pribish, J. R. *J. Org. Chem.* **1983**, *48*, 3613. (m) Tamura, Y.; Akai, S.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1984**, *25*, 1167. (n) Uemura, M.; Minami, T.; Hayashi, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1193. (o) Parker, K. A.; Tallman, E. A. *Tetrahedron* **1984**, *40*, 4781. (p) Tornare, J. M.; Vogel, P. *Helv. Chim. Acta* **1985**, *68*, 1069. (q) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Chem. Lett.* **1986**, 1703.

(5) One-pot Friedel–Crafts cyclizations of two moieties lack regioselectivity. See, e.g.: Wong, C. M.; Popein, D.; Schenk, R.; Te Raa, J. *Can. J. Chem.* **1971**, *49*, 2712. Ishizumi, K.; Ohashi, N.; Tanno, N. *J. Org. Chem.* **1987**, *52*, 4477.

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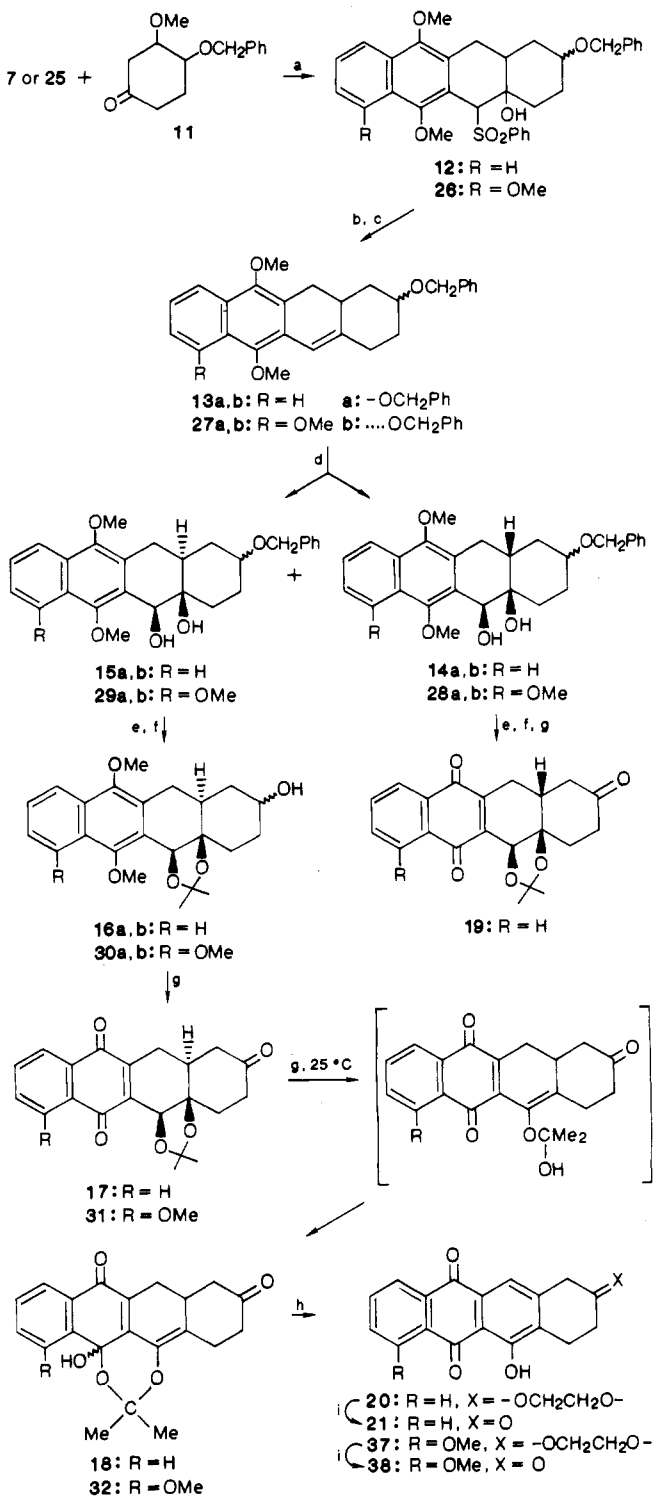
Scheme III[a]



[a] (a) $LiN(SiMe_3)_2$, THF; (b) Na–Hg; (c) $MeO_2CN^-SO_2N^+Et_3$; (d) OsO_4; (e) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH; (f) H_2, Pd–C; (g) CrO_3–DMP; (h) $(CH_2OH)_2$, *p*-TsOH, C_6H_6; (i) CF_3CO_2H–H_2O.

synthesis of the bicyclic bromo sulfone **7** to serve as an annulating reagent for the further elaboration toward a 4-demethoxy model of the target molecule (Scheme I). The readily available 1,4-dimethoxy-2-methyl-3-bromonaphthalene (**3**)[7] afforded, via lithiation and reaction with ethyl chloroformate, the naphthoate **4** (86%), which was converted to the sulfone **6** via reduction to **5** ($LiAlH_4$), bromination (NBS–Me_2S), and treatment of the crude bromide with $PhSO_2Na$ in DMF. Radical bromination proceeds regioselectively at the unsubstituted methyl group of **6** to give the required reagent (**7**) in 78% overall yield from **4**. 2-Carbomethoxy-4,4-(ethylenedioxy)cyclohexanone (**8**),[8] which has the additional protected oxygen functionality required subsequently in ring A of a tetracyclic intermediate, was chosen as a substrate for the bromo sulfone **7** (Scheme II). The above compounds reacted in the presence of an excess of sodium hydride in tetrahydrofuran solution to give, directly, a tetracyclic product **9**, isolated as an amorphous solid (78%), which, on acidification, afforded a single ketone **10**, mp 165 °C (Scheme II). Its stereohomogeneity was evidenced by the proton NMR (270 MHz) spectrum, which showed, inter alia, a single peak for the α-sulfonyl proton at δ 5.22. It was, therefore, assumed that after the initial alkylation step takes place, the aldol-type ring closure occurs diastereoselectively by attack at one face of the ketone due to the coordination of the metal counterion with the oxygens of both sulfone and carbonyl groups, resulting in cis-related SO_2Ph and OH groups in **9**. Indeed, single-crystal analysis of the ketone **10** confirmed this assumption and showed that the angular ester group is also cis-related to the above groups, the A/B rings being cis-fused, with ring A adopting a boat and ring B a half-chair conformation. Further utilization of **10** for the planned synthesis was, however, discontinued in view of the difficulties encountered when attempting to cleave the ester group for subsequent decarboxylation. Acidic and basic hydrolyses, as well as S_N2 conditions, were ineffective and resulted in the recovery of the starting material.

On the basis of our recent findings, regarding the ability of aromatic bromo sulfones to undergo annulations with cycloalkanones devoid of additional activating groups,[9] we turned next to the utilization of 4-(benzyloxy)cyclohexanone (**11**) as an adequate substrate for the bromo sulfone **7** (Scheme III). Thus, addition of an excess of lithium hexamethyldisilazide (LHMDS) to a tetrahydrofuran solution of both **7** and **11** resulted in a chemo- and regioselective two-step process to afford a high yield (92%) of **12** obtained as a mixture of tetracyclic stereoisomers. No intermediate alkylation products were ever detected, the intramolecular aldol type ring closure being probably the faster step in the two-step sequence. A typical reactant ratio of lithium base, ketone **11**, and aromatic reagent **7** was 25:8.3:6.2, and the relative small number of three stereoisomers of **12**, detected by proton NMR and by partial chromatographic separation, was in agreement with the assumed diastereoselective attack of the α-sulfonyl carbanion on the ketone group.[9] Next, modification of ring B had to be effected in order to convert the mixture of tetracyclic stereoisomers **12** into the established precursor of 4-demethoxy-11-deoxydaunomycinone (**21**). A straightforward solution could be provided by oxidative desulfonylation of **12** or of the corresponding allylic sulfone, obtained by dehydration of **12**.[10] Unfortunately, our attempts to apply, in the above systems, the methodology reported for such purposes[11] were entirely unsuccessful. Hence, we submitted the stereoisomeric mixture **12** to an effective sequence, namely, reductive desulfonylation with

(6) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1983**, *24*, 3533.
(7) Adams, R.; Geissman, T. A.; Baker, B. R.; Teeter, H. M. *J. Am. Chem. Soc.* **1941**, *63*, 528.
(8) Lukas, R. M.; Poos, G. I.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1401.
(9) Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1985**, *26*, 6253.
(10) Dehydration occurs by increasing the temperature during the cyclization reaction; see ref 9 for the location of the double bond.
(11) (a) Little, R. D.; Myong, S. O. *Tetrahedron Lett.* **1980**, *21*, 3339. (b) Hwu, J. R. *J. Org. Chem.* **1983**, *48*, 4432.

sodium amalgam,[12] followed by Burgess dehydration[13] to afford a 93% yield of diastereomeric olefins **13a,b**. Introduction of a C-6 hydroxyl group by hydroboration of **13a,b** was attempted next. Although there are reports of successful hydroboration of substituted styrene double bonds,[14] utilization of the BH_3–Me_2S complex or $LiEt_3BH$ as reagents for this purpose and subsequent oxidation afforded, in our hands, even under vigorous conditions, poor yields of the desired alcohol, probably due to the steric hindrance and the presence of electron-releasing substituents in the aromatic ring,[14] and therefore an alternative approach had to be considered. Since epoxidation followed by epoxide opening to an alcohol could be expected to proceed by benzylic C–O bond cleavage at the undesired site, we thought instead to submit the double bond of **13** to hydroxylation, assuming that the formation of secondary–tertiary cis diols would enable selective protection of the secondary hydroxyl and subsequent elimination of the angular hydroxyl group. Treatment with osmium tetraoxide afforded a mixture of stereoisomeric diols (94%), which, due to a significant difference in polarity, could be readily separated into two pairs. The major diol pair (**15a,b**), obtained in 74% yield, was assigned an A/B-trans ring junction, formed by attack of the reagent on the less hindered face of the olefin, to result in a more flattened conformation and, thus, an increased polarity as compared with the minor product (**14a,b**), in which the cis fusion of rings provides a relatively more puckered conformation. Subsequent steps supported these assignments and showed that the components within each pair were C-9 epimers (anthracycline numbering). Attempts to eliminate the tertiary hydroxyl (e.g., via base-induced elimination of the corresponding mesylate) after prior protection of the secondary hydroxyl group in **15a,b** as an acetate resulted, however, in the loss of both oxygen groups and aromatization of ring B. We therefore considered the conversion of ring C into a quinone and thus a change of the electronic effect before attempting to carry out the required transformations in ring B. Accordingly, the diols **15a,b** were protected as acetonides [with $(CH_3)_2C(OCH_3)_2$ and *p*-TsOH] and then debenzylated (H_2, Pd–C) to **16a,b** and the latter subjected to oxidation. When the CrO_3–3,5-dimethylpyrazole (DMP) complex[15,16] was utilized for this purpose, oxidation to the C-9 ketone and concomitant oxidative demethylation of ring C took place and the quinone **17** was formed in 71% yield under relatively mild reaction conditions, at a temperature not exceeding 0 °C.[17] Interestingly, when the above oxidation reaction was allowed to proceed for a longer time, at room temperature, the transformation of **17** into a new, slightly less polar product was observed by TLC. After 48 h this transformation was completed to give a 59% overall yield of **18** in the three-step, one-pot sequence. The enol ether structure assigned to **18** was based on the proton NMR spectrum, which showed the disappearance of the C-6 proton and the presence of a tertiary hydroxyl (singlet at δ 5.34, removable on deuteriation) while two methyl singlets (at δ 1.52 and 1.73) were still present and the molecular weight remained unchanged from that of **17**. The reactivity of the C-5 quinone carbonyl toward nucleophiles (to give **18** via the hemiketal shown in brackets) was evidenced also in a further step (see formation of **39**). The above transformation, useful for our purpose, was found to be specifically induced by the CrO_3–DMP complex and could not be duplicated by utilization of CrO_3–pyridine or by submitting **17** to lithium bases or to DBU.[18] A mechanistic explanation may be based on the favored attack by the basic nitrogen of the CrO_3–DMP complex on the C-6 axial hydrogen, which is probably facilitated by the complexation of the free ligand site of Cr with the π-electrons of the quinone ring.[16] The trans diaxial arrangement of both the C-6 hydrogen and the angular oxygen group, required for such an elimination, is consistent with the stereochemistry assigned to the diols **15a,b**. Indeed, attempts to perform a similar transformation on the acetonide derived from the minor pair of diols (**14a,b**) were unsuccessful, and the end product of the CrO_3–DMP oxidation was, in this case, the quinone **19** exclusively.

Once the problem of elimination of the angular hydroxyl was solved, the elaboration of **21** proceeded without difficulties. An effective cleavage of the enol ether concomitant with dehydrogenation and aromatization of ring B was achieved under ketalization conditions (ethylene glycol, *p*-TsOH) to afford **20** in high yield. Hydrolysis of the ketal by using aqueous trifluoroacetic acid[19] afforded the C-9 ketone **21**.

With a sequence thus available for the conversion of the major diol pair (**15a,b**) into the 4-demethoxy model (**21**) of an established 11-deoxyanthracyclinone intermediate, we undertook the preparation of the bromo sulfone **25**, required as the annulating reagent for the synthesis of **2**. Naphthoate **22**[20] was reduced to alcohol **23**, which was further converted to the bromide (PBr_3) and then to sulfone **24**, which on NBS bromination gave **25**, by a methodology similar to that used in the demethoxy series, in 82% overall yield from **22** (Scheme I). The construction of the tetracyclic framework by the reaction of **25** with 4-(benzyloxy)cyclohexanone (**11**) took place as in the 4-demethoxy series, to afford a stereoisomeric mixture of tetracyclic products of close polarity (**26**, 86%) in which the stereoisomers can be best discerned in the NMR spectrum of the mixture due to the α-sulfonyl protons appearing as singlets at δ 4.93, 4.96, and 5.15. This mixture was submitted to the desulfonylation–dehydration steps, as shown for the 4-demethoxy analogues, to give the olefins **27a,b** (95%) in unequal amounts (78:22). Although chromatographically separable, the isomeric olefin pair was directly submitted to the osmylation step, which, as in the 4-demethoxy series, afforded a mixture of diols (91%), readily separable by chromatography into a minor diol pair (**28a,b**, 22%) and the significantly more polar **29a,b** (69%), to which the trans A/B ring fusion was assigned by analogy.

At this stage, we intended to utilize the previously developed sequence to convert the diols **29a,b** into the precursor **38** and to find, as well, an independent approach for the conversion of the minor diol pair **28a,b** into the same target compound. While diol protection and debenzylation of **29a,b** afforded analogously **30a,b**, the treatment of the latter with CrO_3–DMP resulted in C-9 oxidation and concomitant quinone formation to give **31**, but the expected further conversion to the enol ether **32** could not be brought to completion. The yields of the latter under various reaction conditions did not exceed

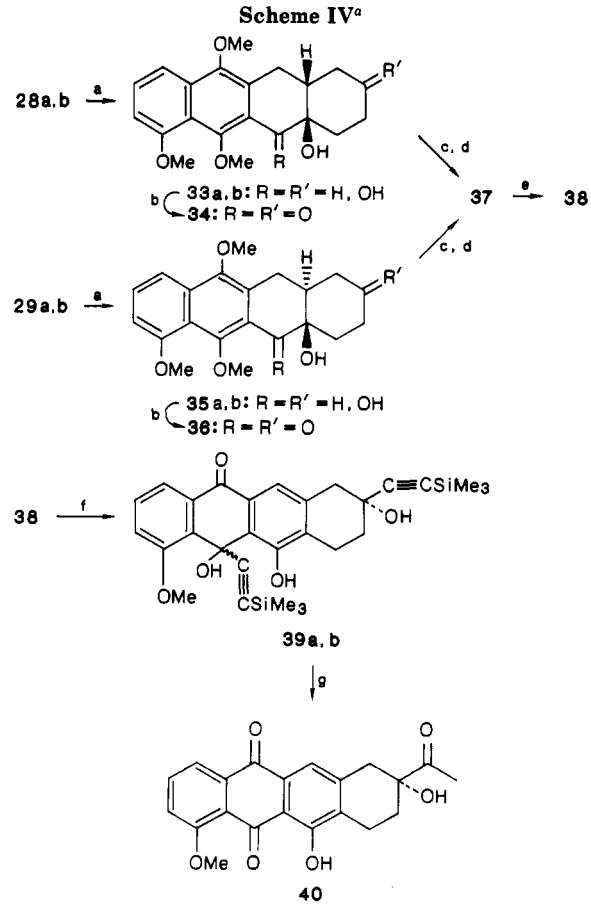
(12) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.
(13) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
(14) See, e.g.: Brown, H. C.; Kim, S. C. *J. Org. Chem.* **1984**, *49*, 1064.
(15) Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499.
(16) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.
(17) The scope of this new mild method of oxidative demethylation has not yet been investigated.
(18) For a similar base-induced opening of a dioxolane ring in a sugar, see: Klemer A.; Rodemeyer, G. *Chem. Ber.* **1974**, *107*, 2612.
(19) Tamura, Y.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. *Tetrahedron* **1984**, *40*, 4539.
(20) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.

20–25%, and the quinone–acetonide **31** was isolated as the major product (in about 40% yield). When the enol ether **32** was submitted to the reaction with CrO_3–DMP, no reconversion to **31** was observed, and therefore, we assume that incomplete transformation is not due to a reversible equilibrium process. A possible explanation to account for the differences in the behavior of **17** and **31** during the reaction with CrO_3–DMP may be based on the interference of the C-4 methoxy group with the required complexation between the CrO_3–DMP reagent and the π-electrons of the quinone, and consequently, the abstraction of the C-6 proton is less effective.

In view of these results, we were faced with the alternative to investigate the possibility of enhancing the dioxolane ring opening by replacing the C-4 methoxy group with a different protecting group or to turn to the utilization of a different approach starting from the diols (**28a,b** and **29a,b**). The first alternative, even if successful, would have diminished the effectiveness of our synthesis, and therefore, we investigated instead the possibility of oxidation of the C-6 hydroxyl group in both diol pairs. Such monooxidations of secondary-tertiary vicinal diols are well-known to present difficulties when manganese dioxide or chromium reagents are used, because of the cleavage of the carbon–carbon bond. Attempts to effect the oxidation by either Cl_2–DMSO or NCS–Me_2S, reagents developed for this specific purpose,[21] were totally unsuccessful, whereas the use of SO_3–pyridine complex or the Fetizon reagent (Ag_2CO_3–Celite), which were reported to effect the monooxidation of primary–tertiary vicinal diols,[22] resulted in the recovery of starting material. Finally, debenzylation (H_2, Pd–$BaSO_4$) and utilization of Swern oxidation conditions[23] on the triols **33** and **35**, respectively, afforded the diketones **34** and **36**, in 81% and 59% yields (Scheme IV). The effectivity of oxidation greatly depended on the utilization of an appropriate excess of oxidation reagents and defined reaction times, as shown in the Experimental Section. The diketones thus obtained were treated with $Ag^{II}O$[24] to afford the corresponding quinones, which were submitted without purification to ketalization conditions, resulting in the selective protection of the C-9 carbonyl and concomitant dehydration, to give **37** in 65% and 71% yields from **34** and **36**, respectively. Hydrolysis with aqueous trifluoroacetic acid produced the ketone **38** in 97% yield. Hence the developed pathway provides the precursor **38** of 11-deoxydaunomycinone in 30% overall yield from bicyclic bromo sulfone **25**.

Further transformation of this precursor into the target molecule (**2**) proceeds via ethynylation of the C-9 ketone. This reaction was reported to give a 30% yield when performed on **38** under optimized conditions[4b] or 25% yield on the 4-hydroxy derivative.[4i] In an attempt to improve these results, we submitted **38** to an excess of reagent formed by treating [(trimethylsilyl)ethynyl]lithium with anhydrous $CeCl_3$. Recently, cerium(III) chloride was found to promote the addition of ethynyl organometallics to carbonyl groups, subject to enolization, and this procedure has been applied in anthracycline synthesis.[25,26] Surprisingly, we obtained two isomeric colorless products, which, although separable by TLC and column chromatography, were almost identical by proton NMR and IR

Scheme IV[a]



[a] (a) H_2, Pd–$BaSO_4$; (b) $(COCl)_2$, DMSO; TEA; (c) $Ag^{II}O$, aqueous HNO_3; (d) $(CH_2OH)_2$, *p*-TsOH, C_6H_6; (e) CF_3COOH–H_2O; (f) $LiC{\equiv}CSIMe_3$ + $CeCl_3$; (g) HgO; H_2SO_4–H_2O, THF.

spectra and by mass spectral fragmentation. These spectroscopic data were consistent with the occurrence of a double ethynylation to give the stereoisomeric **39a,b** in 82% yield, along with 8% of recovered **38**. The regiochemistry of addition to the quinone carbonyl is assigned on the basis of the shift of the phenolic proton in NMR from δ 13.46 (in **38**) to δ 8.39 and 8.43, in **39a** and **39b**, respectively, thus showing the absence of chelated hydroxyl in the addition product. This reactivity of the quinone carbonyl, which seems to be connected with the absence of 11-hydroxyl, was recently mentioned by Tamura as an obstacle for the elaboration of 11-deoxyanthracyclinones from C-9 ketones by use of Ce(III) organometallics in the above series, in contrast to the behavior of 11-hydroxy analogues.[27] We found, however, that on hydration of **39a,b** (HgO, aqueous H_2SO_4, THF) the undesired ethynylation is reversible and the quinone moiety is regenerated, whereas the C-9 ethynyl group is converted to the acetyl group, to give **40** in 58% yield, with physical and spectroscopic data identical with those reported.[4f,p] Since **40** has been converted via C-7 bromination into the target molecule **2**,[4b,f] our route represents a new synthesis of 11-deoxydaunomycinone, which can also be extended to other 11-deoxyanthracyclinones.

Experimental Section

Melting points were determined on a Reichert hot-stage microscope and are uncorrected. ^1H NMR spectra were recorded

(21) Corey, E. J.; Kim, C. U. *Tetrahedron Lett.* **1974**, 287.
(22) Tanno, N.; Terashima, S. *Chem. Pharm. Bull.* **1983**, *31*, 811.
(23) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(24) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227.
(25) Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531.
(26) Tamura, Y.; Sasho, M.; Akai, S.; Kisimoto, H.; Sekihachi, J.; Kita, Y. *Tetrahedron Lett.* **1986**, *27*, 195.
(27) Tamura, Y.; Sasho, M.; Ohe, H.; Akai, S.; Kita, Y. *Tetrahedron Lett.* **1985**, *26*, 1549, footnote 6. **Note added in proof**: After the completion of our work, a similar formation of **39a,b** via double ethynylation of **38** came to our attention. See: Tamura, Y.; Akai, S.; Kishimoto, H.; Kirihara, M.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1987**, *28*, 4583.

in $CDCl_3$ on Varian T-80 or Bruker 270-MHz instruments and referenced to Me_4Si as an internal standard. Merck silica gel 60 was used for column chromatography, and TLC data were obtained with precoated Merck 60F-254 silica gel on aluminum sheets. All air- and moisture-sensitive reactions were carried out in flame-dried, argon-flushed, two-necked flasks, sealed with rubber septa, and the reagents were introduced via a syringe. THF was freshly distilled from sodium–benzophenone under nitrogen.

1,4-Dimethoxy-3-(ethoxycarbonyl)-2-methylnaphthalene (4). To a cooled (−78 °C) solution of 1,4-dimethoxy-2-methyl-3-bromonaphthalene[7] (**3**) (0.562 g, 2 mmol) in anhydrous THF (12 mL) was added dropwise a solution of 1.6 M *n*-butyllithium in hexane (1.5 mL, 2.4 mmol) during 5 min. After the mixture was stirred for 30 min, ethyl chloroformate (0.405 g, 3.75 mmol) was added dropwise and the mixture was stirred at −78 °C for 15 min, then poured onto crushed ice and 10% aqueous HCl, and extracted with ether containing 10% $CHCl_3$. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo, and the residue was flash chromatographed (pentane–ether, 9:1) to afford **4** (0.47 g, 86%) as an oil (lit.[28] oil): ^1H NMR δ 1.42 (t, 3 H), 2.38 (s, 3 H), 3.86 (s, 3 H), 3.98 (s, 3 H), 4.38 (q, 2 H), 7.44–7.56 (m, 2 H), 8.01–8.13 (m, 2 H). Anal. Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 70.42; H, 6.59.

1,4-Dimethoxy-3-(hydroxymethyl)-2-methylnaphthalene (5). The ester **4** (0.61 g, 2.2 mmol) was dissolved in dry ethyl ether (20 mL) and added dropwise to an ice-cooled suspension of $LiAlH_4$ (0.15 g, 3.95 mmol) in dry THF (20 mL). The mixture was stirred for 1 h at 25 °C, then treated successively with aqueous saturated Na_2SO_4 solution and powdered Na_2SO_4, filtered, and evaporated. The residue was crystallized by trituration with pentane to give 0.486 g of **5** (94%): mp 119–120 °C (from ether–hexane); ^1H NMR δ 2.51 (s, 3 H), 3.87 (s, 3 H), 3.97 (s, 3 H), 4.93 (br s, 2H), 7.43–7.56 (m, 2 H), 8.01–8.14 (m, 2 H). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.46; H, 7.05.

1,4-Dimethoxy-2-methyl-3-[(phenylsulfonyl)methyl]-naphthalene (6). To a cold (0 °C) stirred solution of NBS (0.592 g, 3.32 mmol) in dry CH_2Cl_2 (12 mL) was added dropwise Me_2S (0.275 mL, 3.75 mmol) under argon. After 10 min, the reaction mixture was cooled to −20 °C and a solution of the alcohol **5** (0.464 g, 2 mmol) and dry THF (6 mL) was added dropwise. The resulting mixture was stirred for 3 h, being allowed to warm gradually to 10 °C, then poured into ice-cold brine, and extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was dissolved in DMF (9 mL), then $PhSO_2Na$ (0.36 g, 2.2 mmol) was added, and the resulting solution was stirred at room temperature for 2 h and then poured into water and ice. After standing overnight, the crystals were filtered and dried to give 0.63 g (89%) of **6**. An analytical sample had mp 132–133 °C ($CHCl_3$–hexane); ^1H NMR δ 2.40 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.69 (s, 2 H), 7.40–8.03 (m, 9 H). Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.42; H, 5.62. Found: C, 67.32; H, 5.50.

1,4-Dimethoxy-2-(bromomethyl)-3-[(phenylsulfonyl)-methyl]naphthalene (7). A mixture of sulfone **6** (0.62 g, 1.74 mmol), NBS (0.31 g, 1.74 mmol), and benzoyl peroxide (60 mg) in CCl_4 (40 mL) was refluxed under illumination for 30 min, with TLC monitoring. After cooling, the reaction mixture was filtered, concentrated in vacuo, and chromatographed (elution with pentane–ether, 2:1, containing 5% CH_2Cl_2) to give 0.704 g of bromo sulfone **7** (93%): mp 140 °C ($CHCl_3$–hexane); ^1H NMR δ 3.85 (s, 3 H), 4.04 (s, 3 H), 4.84 (s, 2 H), 5.15 (s, 2 H), 7.44–8.06 (m, 9 H). Anal. Calcd for $C_{20}H_{19}BrO_4S$: C, 55.17; H, 4.37. Found: C, 55.29; H, 4.42.

6,11-Dimethoxy-4a-hydroxy-12a-(methoxycarbonyl)-2-oxo-5-(phenylsulfonyl)-1,2,3,4,4a,5,12,12a-octahydronaphthacene (10). A solution of 0.107 g (0.5 mmol) of 2-(methoxycarbonyl)-4,4-(ethylenedioxy)cyclohexanone (**8**)[8] in dry THF (8 mL) was added to a reaction flask containing NaH (80% oil dispersion, washed with dry pentane, net weight 96 mg, 4 mmol) under argon. After the mixture was stirred for 30 min at 25 °C, it was cooled to 0 °C and a solution of bromo sulfone **7** (0.109 g, 0.25 mmol) in dry THF (5 mL) was added dropwise. The mixture was stirred at 0 °C for 6 h (TLC monitoring), the poured onto aqueous NH_4Cl and ice, and extracted with chloroform. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. Chromatography (ether–pentane, 2:1) gave first the recovered excess of ketone **8** (40 mg) and then 0.11 g of **9** (78%, calculated on the basis of **7**) as an amorphous solid: ^1H NMR δ 1.48–2.57 (m, 8 H), 3.54 (s, 3 H), 3.79 (s, 3 H), 3.85–3.90 (br s, 4 H), 3.95 (s, 3 H), 4.89 (s, 1 H), 6.10 (br, OH), 7.29–8.09 (m, 9 H). This product was dissolved in THF (10 mL) to which aqueous 10% HCl (2 mL) was added and the mixture stirred for 5 h and worked up to give **10** (96 mg, 95%). An analytical sample had mp 165 °C ($CHCl_3$–hexane: ^1H NMR (270 MHz) δ 1.74–2.20 (m, 3 H), 1.93 (d, J = 16 Hz, 1 H), 2.50 (d, J = 16 Hz, 1 H), 2.72 (m, 1 H), 3.12 (d, J = 16 Hz, 1 H), 3.80 (s, 3 H), 3.84 (s, 3 H), 3.88 (s, 3 H), 4.10 (d, J = 16 Hz, 1 H), 5.20 (br s, OH), 5.22 (s, 1 H), 7.43–8.11 (m, 9 H). Anal. Calcd for $C_{28}H_{28}O_8S$: C, 64.12; H, 5.34. Found: C, 64.49; H, 5.22.

2-(Benzyloxy)-6,11-dimethoxy-4a-hydroxy-5-(phenylsulfonyl)-1,2,3,4,4a,5,12,12a-octahydronaphthacene (12, Stereoisomeric Mixture). To a solution of freshly distilled hexamethyldisilazane (6.25 mL, 28 mmol) in anhydrous THF (75 mL) was added *n*-butyllithium (25 mmol) in hexane (17 mL) under an argon atmosphere at 0 °C. After the mixture was stirred for 15 min, the above-prepared LHMDS was introduced in three portions, during 45 min, via syringe, through a septum cap, into a two-neck reaction flask containing a (cooled to −78 °C) solution of 4-(benzyloxy)cyclohexanone[29] (**11**, 1.7 g, 8.3 mmol), bromo sulfone **7** (2.7 g, 6.2 mmol), and 2,2′-bipyridine (10 mg, as indicator for base) in anhydrous THF (250 mL), under argon. After being stirred for 1 h at −78 °C, the reaction mixture was slowly warmed to 0 °C (1 h), then poured onto ice and aqueous (10%) HCl, and extracted (3×) with ether containing 20% $CHCl_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo, and the residue was flash chromatographed (pentane–ether, 1:1, then 1:3) to give **12** (3.18 g, 92%) as a stereoisomeric mixture, which was used in the further step without separation. Partial chromatographic separation of stereoisomers, for spectral identification, gave first an oil (1.42 g): homogeneous by TLC; ^1H NMR δ 1.80–2.59 (m, 10 H), 3.67 (s, 3 H), 3.76 (s, 3 H), 3.72–3.90 (m, 1 H), 4.42 (s, 2 H), 5.04 (s, 1 H), 7.32–8.01 (m, 14 H); MS, m/e (relative intensity) 558 (M^+) (4), 416 (56) ($M^+ - HSO_2Ph$), 398 (24).

The next fraction was an inseparable crystalline mixture (~1:1) of two stereoisomers (1.75 g): ^1H NMR δ 1.72–3.48 (m, 10 H), 3.50, 3.68, 3.74, and 3.83 (4 s, two pairs of CH_3, 6 H), 3.86–4.02 (m, 1 H), 4.55 (s, 2 H), 4.80 and 5.03 (2 s, 1 H, $CHSO_2Ph$), 7.15–7.99 (m, 14 H); MS, m/e (relative intensity) 558 (M^+) (3), 416 (100) ($M^+ - HSO_2Ph$).

2-(Benzyloxy)-6,11-dimethoxy-1,2,3,4,12,12a-hexahydronaphthacene (13a,b). To a solution of **12** (3.2 g, 5.73 mmol, stereoisomeric mixture) in anhydrous THF (50 mL) and MeOH (110 mL) were added Na_2HPO_4 (5.8 g) and 6% pulverized Na–Hg amalgam (12 g). After being stirred for 3 h at room temperature (TLC monitoring), the reaction mixture was diluted with ice-cold brine and extracted with ether containing 20% $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue, which was directly dissolved in dry benzene (120 mL) and added to the Burgess reagent,[13] freshly prepared from carbomethoxysulfamoyl chloride (5 g, 29 mmol) in benzene solution (50 mL). After 1 h of stirring at 50 °C, TLC showed the formation of two fluorescent nonpolar products (R_f 0.7 and 0.4 in cyclohexane–ethyl acetate, 6:1). Addition of brine and extraction with ether gave, after evaporation of the solvent and chromatography of the residue (pentane–ether, 9:1), 2.133 g (93%) of a pair of stereoisomers **13a** and **13b**, which was used directly for the next step. Partial chromatographic separation for identification gave the less polar (~75% of the total) fraction (**13a** or **13b**): mp 92–93 °C; ^1H NMR δ 1.41–1.68 (m, 1 H), 2.14–2.92 (m, 7 H), 3.30–3.41 (m, 1 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 3.88–4.10 (m, 1 H), 4.57 (s, 2 H), 6.69–6.71 (br s, 1 H), 7.28–8.10 (m, 9 H); MS, m/e (relative intensity) 400 (M^+) (100), 383 (72), 277 (64).

The polar (minor) product (**13a** or **13b**) was an oil: ^1H NMR δ 1.73–2.75 (m, 8 H), 3.43–3.62 (m, 1 H), 3.86 (s, 3 H), 3.89 (s, 3

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H), 3.90–4.09 (m, 1 H), 4.63 (s, 2 H), 6.70–6.72 (br s, 1 H), 7.28–8.10 (m, 9 H); MS, *m/e* (relative intensity), 400 (M^+) (100), 383 (42), 277 (65).

2-(Benzyloxy)-6,11-dimethoxy-4aβ,5β-dihydroxy-1,2,3,4,4a,5,12,12aβ-octahydronaphthacene (14a,b) and 2-(Benzyloxy)-6,11-dimethoxy-4aβ,5β-dihydroxy-1,2,3,4,4a,5,12,12aα-octahydronaphthacene (15a,b). To a solution of **13a,b** (2.08 g, 5.2 mmol) in dry pyridine (60 mL) was added a solution of OsO_4 (2 g, 7.87 mmol) in anhydrous THF (50 mL), and the mixture was allowed to stand for 48 h in the dark, with occasional stirring, at 25 °C. Aqueous $NaHSO_3$ (8 g in 60 mL of H_2O) was then added, and the resulting mixture was stirred for 3 h at room temperature, then diluted with water, and extracted with EtOAc (3×). The combined organic layers were washed successively with aqueous (10%) HCl and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give a residue, which was chromatographed. Elution with pentane–ether (2:1, then 1:1) gave 0.453 g (20%) of a crystalline fraction (**14a,b**, two close spots in TLC), and then on elution with ether containing 20% EtOAc was obtained **15a,b** as the main crystalline fraction (1.67 g, 74%). Each of the two fractions was used without further separation in the next steps. Recrystallization of each fraction ($CHCl_3$–hexane) afforded the pure major epimers for spectral identification. The major epimer of **14a,b** (~75% of the total) had mp 188–190 °C: ^1H NMR δ 1.94–3.84 (m, 12 H), 3.88 (s, 3 H), 3.98 (s, 2 H), 4.55 (s, 2 H), 4.88 (s, 1 H), 5.13 (s, 1 H), 7.29–8.07 (m, 9 H); MS, *m/e* (relative intensity) 434 (M^+) (100), 416 (34), 385 (14), 325 (15). The minor epimer (~25%) could not be separated in pure form and exhibited similar peaks in ^1H NMR, except at δ 4.64 (s, 2 H) and 4.78 (s, 1 H).

The major epimer of **15a,b** (~80% of the total) had mp 130–131 °C: ^1H NMR δ 1.71–3.80 (m, 12 H), 3.86 (s, 3 H), 4.00 (s, 3 H), 4.56 (s, 2 H), 5.02 (s, 1 H), 7.29–8.10 (m, 9 H); MS, *m/e* (relative intensity) 434 (M^+) (100), 416 (38), 385 (23), 293 (25). The minor epimer (~20%) could not be separated in pure form and had a similar ^1H NMR spectrum, except at δ 3.84 (s, 3 H), 4.01 (s, 3 H), 4.53 (s, 2 H), and 5.24 (s, 1 H).

4aβ,5β-(Isopropylidenedioxy)-1,2,3,4,4a,5,12,12aα-octahydro-2,6,11-naphthacenetrione (17) and 5-(2-Hydroxyisopropoxy)-1,2,3,4,12,12a-hexahydro-2,6,11-naphthacenetrione (18). To a solution of the diols (**15a,b**, 0.835 g, 1.9 mmol) in dry CH_2Cl_2 (20 mL) and DMF (8.5 mL) were added 2,2-dimethoxypropane (8 mL) and *p*-TsOH (0.1 g), and the resulting mixture was stirred at 25 °C for 2 h (TLC monitoring). Aqueous $NaHCO_3$ was then added, and the mixture was extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo, and the product was separated from excess reagent by flash chromatography (pentane–ether, 4:1), then dissolved in ethyl acetate (80 mL), and stirred under hydrogen with 10% Pd on carbon (0.2 g) as a catalyst. After 2 h (TLC monitoring), the catalyst was filtered and washed with hot ethyl acetate and the filtrate, on evaporation, gave a crystalline mixture of **16a** and **16b** epimers (0.66 g, 89%): ^1H NMR δ 1.17, 1.34, 1.55, and 1.84 (4 s, 6 H, two pairs of CH_3), 2.21–3.74 (m, 11 H), 3.87 (s, 3 H), 4.07 (s, 3 H), 5.29 and 5.52 (2 s, 1 H, two epimers), 7.42–8.12 (m, 4 H). Without further characterization, the above acetonides (85 mg, 0.22 mmol) were dissolved in dry CH_2Cl_2 (10 mL) and added by syringe via septum cap under argon to a CrO_3–3,5-dimethylpyrazole (DMP) complex, prepared from freshly dried CrO_3 (0.6 g, 6 mmol) and DMP (0.576 g, 6 mmol) at −20 °C in dry CH_2Cl_2 (5 mL). The resulting mixture was stirred for 2 h, and the temperature was allowed to rise gradually to 0 °C. The reaction mixture was then poured over aqueous $NaHCO_3$ and extracted (3×) with $CHCl_3$. The combined organic layers were washed with aqueous (10%) HCl and brine, dried (Na_2SO_4e, and flash chromatographed (pentane–ether, 2:1, with 5% CH_2Cl_2) to give **17** as yellow crystals (55 mg, 71%). An analytical sample had mp 188–190 °C: IR (KBr) 1711, 1667, 1631, and 1593 cm^{-1}; ^1H NMR δ 1.26 (s, 3 H), 1.60 (s, 3 H), 1.82–3.08 (m, 9 H), 4.94 (s, 1 H), 7.72–7.79 (m, 2 H), 8.06–8.16 (m, 2 H); MS, *m/e* (relative intensity) 353 ($M^+ + 1$) (13), 337 (87), 277 (100), 235 (29).

In a separate analogous oxidation experiment with the same amounts of reagents, the reaction mixture after 2 h was allowed to warm to room temperature and stirred under argon for 48 h. TLC monitoring showed the conversion of **17** to a new, slightly less polar product which, instead of the yellow spot of **17**, produces a strongly darkening spot on TLC. Workup as for **17** afforded **18** as colorless (yellow in air) crystals (46 mg, 59% from **16a,b**). An analytical sample had mp 156–157 °C ($CHCl_3$–hexane): IR (KBr) 1713, 1667, and 1593 cm^{-1}; UV (EtOH) λ_{max} 247 (ε = 17 600), 267 (11 200), 338 (3200) nm; ^1H NMR (270 MHz) δ 1.52 (s, 3 H), 1.73 (s, 3 H), 1.80–1.94 (m, 1 H), 1.97–3.11 (m, 8 H), 5.34 (s, OH), 7.71–7.79 (m, 2 H), 8.05–8.16 (m, 2 H); MS, *m/e* (relative intensity) 353 ($M^+ + 1$) (77), 337 (20), 310 (60), 295 (17), 251 (36), 237 (50), 199 (100).

4aβ,5β-(Isopropylidenedioxy)-1,2,3,4,4a,5,12,12aβ-octahydro-2,6,11-naphthacenetrione (19). The three-step sequence described above for the preparation of **17** from **15a,b** was used on **14a,b** under similar reaction conditions except that the formation of acetonide required 10 h. Compound **19** was obtained in 53% overall yield, as pale yellow crystals: mp 198–199 °C; IR 1717, 1667, 1629, and 1594 cm^{-1}; ^1H NMR δ 1.25 (s, 3 H), 1.56 (s, 3 H), 1.69–2.81 (m, 9 H), 5.23 (sps, 1 H), 7.68–7.80 (m, 2 H), 8.05–8.20 (m, 2 H); MS, *m/e* (relative intensity), 353 ($M^+ + 1$) 6, 337 (89), 277 (100).

In a separate experiment, the oxidation with CrO_3–DMP complex was continued at room temperature for 48 h. No change in TLC was observed, and **19** was the sole product isolated after workup.

2,2-(Ethylenedioxy)-5-hydroxy-1,2,3,4-tetrahydro-6,11-naphthacenedione (20). A mixture of **18** (84 mg, 0.24 mmol), ethylene glycol (1.6 mL), and *p*-TsOH (a few crystals) in benzene (8 mL) was refluxed for 6 h with azeotropic removal of water by Dean–Stark apparatus. After cooling, the mixture was diluted with $CHCl_3$ (40 mL), washed with aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give yellow crystals of **20** (76 mg, 95%): mp 220–222 °C; IR 1670, 1631, 1591 cm^{-1}; ^1H NMR (270 MHz) δ 1.99 (t, *J* = 7 Hz, 2 H), 3.01 (t, *J* = 7 Hz, 2 H), 3.06 (s, 2 H), 4.05 (s, 4 H), 7.50 (s, 1 H), 7.75–7.79 (m, 2 H), 8.23–8.29 (m, 2 H), 13.1 (s, 1 H); MS, *m/e* (relative intensity) 336 (M^+) (100), 275 (10), 264 (88), 250 (75).

5-Hydroxy-1,2,3,4-tetrahydro-2,6,11-naphthacenetrione (21). The ketal **20** (34 mg, 0.1 mmol) was suspended in a solution of CF_3COOH and water (1:1, 2 mL), the mixture was stirred at room temperature for 6 h and then diluted with $CHCl_3$, and the organic layer was washed several times with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to give **21** as orange crystals (27 mg, 92%). An analytical sample had mp 248–250 °C (lit.[4a] mp 245–247 °C); IR (KBr) 1727, 1668, 1630 cm^{-1}; ^1H NMR (270 MHz) δ 2.62 (t, *J* = 7 Hz, 2 H), 3.35 (t, *J* = 7 Hz, 2 H), 3.66 (s, 2 H), 7.61 (s, 1 H), 7.80–7.84 (m, 2 H), 8.28–8.34 (m, 2 H), 12.95 (s, 1 H); MS, *m/e* (relative intensity), 292 (74), 264 (40), 250 (100).

3-(Hydroxymethyl)-2-methyl-1,4,5-trimethoxynaphthalene (23). 3-(Ethoxycarbonyl)-2-methyl-1,4,5-trimethoxynaphthalene (**22**)[20] was reduced by $LiAlH_4$ as shown for **4**. Purification by column chromatography (pentane–ether, 2:1) gave **23** (90%): mp 114–116 °C ($CHCl_3$–hexane); ^1H NMR δ 2.48 (s, 3 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.00 (s, 3 H), 4.89 (s, 2 H), 6.85 (d, *J* = 9 Hz, 1 H), 7.26–7.75 (m, 2 H). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.76; H, 6.88.

2-Methyl-3-[(phenylsulfonyl)methyl]-1,4,5-trimethoxynaphthalene (24). To a cooled solution (−5 °C) of **23** (0.47 g, 1.8 mmol) in anhydrous CH_2Cl_2 was added freshly distilled PBr_3 (0.2 mL, 2.1 mmol), and the mixture was stirred for 10 min at −5 °C, then poured over ice and aqueous $NaHCO_3$, and extracted with ether containing 20% $CHCl_3$. The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was dissolved in DMF (9 mL), then $PhSO_2Na$ (0.33 g, 2 mmol) was added, and the mixture was stirred for 1 h at room temperature, then diluted with water, and worked up as above. Chromatography (pentane–ether, 1:1) gave **24** (0.64 g, 93%): mp 105–107 °C ($CHCl_3$–hexane); ^1H NMR δ 2.37 (s, 3 H), 3.73 (s, 3 H), 3.81 (s, 3 H), 3.91 (s, 3 H), 4.72 (s, 2 H), 6.84 (d, *J* = 8 Hz, 1 H), 7.28–7.89 (m, 7 H). Anal. Calcd for $C_{21}H_{22}SO_5$: C, 65.28; H, 5.70. Found: C, 65.51; H, 5.58.

2-(Bromomethyl)-3-[(phenylsulfonyl)methyl]-1,4,5-trimethoxynaphthalene (25) was prepared from **24** as shown for **7** in 98% yield: mp 196–198 °C ($CHCl_3$–hexane); ^1H NMR δ 3.75 (s, 3 H), 3.91 (s, 3 H), 4.01 (s, 3 H), 4.89 (s, 2 H), 5.11 (s, 2 H), 6.91 (d, *J* = 8 Hz, 1 H) 7.29–7.94 (m, 7 H). Anal. Calcd for $C_{21}H_{21}BrSO_5$: C, 56.34; H, 5.44. Found: C, 56.12; H, 5.31.

2-(Benzyloxy)-6,7,11-trimethoxy-1,2,3,4,12,12a-hexahydronaphthacene (27a and 27b, Diastereomers). The bromo sulfone **25** (2.435 g, 5.2 mmol) was reacted with 4-(benzyloxy)-cyclohexanone (**11**, 1.385 g, 6.8 mmol) as described for the preparation of **12**, with an increase of reaction time: LHMDS was added at −78 °C during 1 h, and then the temperature was slowly increased to −20 °C (1 h) and further to 0 °C (1 h). Chromatography (pentane–ether, 1:1, and 10% CH_2Cl_2) gave 2.65 g of **26** (86%) as a stereoisomeric mixture (three spots of similar polarity in TLC); ^1H NMR spectrum contains signals at δ 4.93, 4.96, and 5.15 (3 s, 1 H). The mixture was submitted, without characterization, to 6% Na–Hg amalgam and then to Burgess reagent, as described for the preparation of **13a,b**, to give 1.84 g of **27a,b** (95%, or 82% overall yield calculated on the basis of **25**). The above olefins (two fluorescent spots in TLC, R_f 0.6 and 0.7, in cyclohexane–ethyl acetate, 5:1) were used directly in the further step without separation. For spectroscopic identification, they were separated once by flash chromatography (elution with pentane and 15% ether) to give the less polar fraction (1.41 g, **27a** or **27b**): mp 112–113 °C; ^1H NMR δ 1.66–3.37 (m, 9 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 3.85–4.08 (m, 1 H), 3.97 (s, 3 H), 4.57 (s, 2 H), 6.75–6.85 (m, 2 H), 7.20–7.69 (m, 7 H); MS, *m/e* (relative intensity) 430 (M^+) (100), 322 (63), 307 (60). Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.14; H, 6.98. Found: C, 78.29; H, 7.02. The next eluted fraction, 0.41 g (**27a** or **27b**), had mp 167–168 °C: ^1H NMR δ 1.62–3.57 (m, 9 H), 3.78 (s, 3 H), 3.82 (s, 3 H), 3.85–4.02 (m, 1 H), 3.98 (s, 3 H), 4.62 (s, 2 H), 6.75–6.86 (m, 2 H), 7.21–7.68 (m, 7 H); MS, *m/e* (relative intensity) 430 (M^+) (100), 307 (30). Anal. Calcd for $C_{28}H_{30}O_4$: C, 78.14; H, 6.98. Found: C, 78.36; H, 6.98.

2-(Benzyloxy)-4aβ,5β-dihydroxy-6,7,11-trimethoxy-1,2,3,4,4a,5,12,12aβ-octahydronaphthacene (28a,b) and 2-(Benzyloxy)-4aβ,5β-dihydroxy-6,7,11-trimethoxy-1,2,3,4,4a,5,12,12aα-octahydronaphthacene (29a,b). The olefins **27a,b** (1.58 g, 3.67 mmol) were reacted with OsO_4 as described for **13a,b** and afforded by chromatography in the first fraction (pentane–ether, 1:1, and 10% CH_2Cl_2) the diols **28a,b**, 0.37 g (22%), and further, on elution with ether–ethyl acetate, 4:1, were obtained the diols **29a,b** (1.17 g, 69%). Although each fraction was used directly in the following steps, flash chromatographic separation was effected once, for spectroscopic identification. The first eluted fraction (pentane–ether, 1:1, **28a** or **28b**, ~80% of the epimeric pair) had mp 161–162 °C: ^1H NMR δ 1.62–3.45 (m, 10 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 3.82–3.98 (m, 1 H), 4.01 (s, 3 H), 4.55 (s, 2 H), 4.86 (s, 1 H), 5.17 (br, 1 H), 6.83 (d, J = 8 Hz, 1 H), 7.28–7.67 (m, 7 H); MS, *m/e* (relative intensity) 464 (M^+) (100), 446 (19), 323 (25). The next fraction (same eluent, ~20% of the epimeric pair, **28a** or **28b**) had mp 167–169 °C: ^1H NMR was nearly identical with the above, except at δ 4.63 (s, 2 H, CH_2Ph) and 4.77 (s, 1 H, C*H*OH); MS, *m/e* (relative intensity) 464 (M^+) (100), 446 (18), 340 (19), 323 (19). The next eluted fraction (ether–ethyl acetate, 4:1, **29a** or **29b**, ~15% of the epimeric pair) had mp 192–194 °C: ^1H NMR δ 1.59–3.82 (m, 11 H), 3.83 (s, 3 H), 3.89 (s, 3 H), 4.00 (s, 3 H), 4.53 (s, 2 H), 5.23 (s, 1 H), 6.82 (d, J = 7 Hz, 1 H), 7.29–7.71 (m, 7 H); MS, *m/e* (relative intensity) 464 (M^+) (100), 446 (31), 356 (22). The last eluted fraction (**29a** or **29b**, ~85% of the epimeric pair) had mp 148 °C: ^1H NMR was nearly identical with the above, except at δ 4.56 (s, 2 H, CH_2Ph) and 5.02 (s, 1 H); MS, *m/e* (relative intensity) 464 (M^+) (100), 446 (50), 317 (37).

4aβ,5β-(Isopropylidenedioxy)-7-methoxy-1,2,3,4,4a,5,12,12aα-octahydro-2,6,11-naphthacenetrione (31) and 5-(2-Hydroxyisopropoxy)-7-methoxy-1,2,3,4,12,12a-hexahydro-2,6,11-naphthacenetrione (32). The epimeric crystalline diol pair **29a,b** (0.232 g, 0.5 mmol) was converted, as shown for **15a,b**, to the crystalline **30a,b** (0.18 g, 87%): ^1H NMR δ 1.34 (s, 3 H), 1.53 (s, 3 H), 1.67–3.18 (m, 10 H), 3.83 (s, 3 H), 3.93 (s, 3 H), 4.00 (s, 3 H), 4.35–4.52 (m, 1 H), 5.32 and 5.55 (2 s, ~4:1, 1 H, epimeric C*H*O), 6.82 (d, J = 8 Hz, 1 H), 7.29–7.78 (m, 2 H). Without further characterization, 0.18 g (0.43 mmol) of **30a,b** was reacted with CrO_3–DMP complex, as described for **16a,b**. After 30 h, similar workup and chromatography (pentane–ether, 1:1, and 10% CH_2Cl_2) afforded first **32** (35 mg, 21%) as colorless crystals: mp 151–152 °C; IR (KBr) 1715, 1653, 1636, 1587 cm^{-1}; ^1H NMR δ 1.50 (s, 3 H), 1.71 (s, 3 H), 1.82–3.08 (m, 9 H), 4.02 (s, 3 H), 5.53 (br s, OH), 7.28–7.74 (m, 3 H); MS, *m/e* (relative intensity) 383 (M^+ + 1), (28), 340 (35), 323 (92). The compound **31** (66 mg, 40%) was eluted next as yellow crystals: mp 197–198 °C; IR (KBr) 1716, 1660, 1587 cm^{-1}; ^1H NMR δ 1.52 (s, 3 H), 1.57 (s, 3 H), 1.80–2.90 (m, 9 H), 3.99 (s, 3 H), 4.94 (s, 1 H), 7.29–7.73 (m, 3 H); MS, *m/e* (relative intensity) 383 (M^+ + 1) (31), 367 (27), 324 (100), 307 (89), 265 (29).

5β-Hydroxy-6,7,11-trimethoxy-1,2,3,4,4a,5,12,12aβ-octahydro-2,5-naphthacenedione (34). To a solution of diols **28a,b** (0.524 g, 1.13 mmol) dissolved in absolute methanol (80 mL) was added 5% Pd on $BaSO_4$ (0.35 g), andthe mixture was stirred under hydrogen at atmospheric pressure. After 2.5 h (TLC monitoring), the catalyst was filtered and washed with hot methanol. The filtrate was evaporated in vacuo to give **33a,b** (0.405 g, 96%) as a white crystalline mixture (R_f 0.3 and 0.4 in ethyl acetate–cyclohexane, 3:1) with the less polar epimer as the main component: ^1H NMR δ 1.57–2.05 (m, 8 H), 2.80 (d, J = 7 Hz, 2 H), 3.84 (s, 3 H), 3.89 (s, 3 H), 4.0 (s, 3 H), 4.20 (br s, 2 H), 4.86 (s, 1 H), 5.25 (br s, 1 H), 6.84 (d, J = 7.5 Hz, 1 H), 7.38–7.71 (m, 2 H). This epimeric mixture was used without further characterization or purification in the next step. To a stirred solution of 0.6 mL (6.6 mmol) of oxalyl chloride in CH_2Cl_2 (12 mL) in a two-neck flask under argon at −60 °C was added a solution of 1 mL of DMSO (13 mmol) in CH_2Cl_2 (3 mL). After the mixture was stirred for 3 min, a solution of 0.1 g (0.26 mmol) of **33a,b** in CH_2Cl_2 (6 mL) was added dropwise, via syringe. The mixture was stirred for 45 min at −60 °C, and 4.2 mL (30 mmol) of triethylamine was then added. After being stirred for an additional 15 min, the mixture was slowly warmed to room temperature. Brine was added, the organic layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo, and the residue was flash chromatographed (ether–pentane, 3:1, and 5% CH_2Cl_2) to afford 80 mg (81%) of **34** as white crystals. An analytical sample had mp 210–211 °C ($CHCl_3$–hexane): IR (KBr) 1715, 1685, 1613, 1559 cm^{-1}; ^1H NMR δ 1.71–3.10 (m, 9 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 3.98 (s, 3 H), 4.45 (br, 1 H), 6.85 (dd, J = 1.5, 7 Hz, 1 H), 7.40–7.71 (m, 2 H); MS, *m/e* (relative intensity) 370 (M^+) (100), 337 (33), 309 (14).

2,2-(Ethylenedioxy)-5-hydroxy-7-methoxy-1,2,3,4-tetrahydro-6,11-naphthacenedione (37) and 5-Hydroxy-7-methoxy-1,2,3,4-tetrahydro-2,6,11-naphthacenetrione (38). To a stirred solution of **34** (0.27 g, 0.73 mmol) in pure acetone (30 mL) were added 0.35 g of $Ag^{II}O$ (2.8 mmol)[24] and 1.5 mL of 1.6 M HNO_3 solution (2.4 mmol). The mixture became green and homogeneous. After 15 min, the solution was diluted with H_2O and $CHCl_3$. The organic layer was separated, and the aqueous layer was extracted several times with $CHCl_3$ until the extract was colorless. The combined organic layers were dried (Na_2SO_4), filtered, and evaporated in vacuo. Anhydrous benzene (40 mL), ethylene glycol (4 mL), and a few crystals of *p*-toluenesulfonic acid were added to the poorly soluble residue, and the mixture was refluxed with azeotropic removal of water by a Dean–Stark apparatus. The orange-colored suspension slowly dissolved, and after 3.5 h, the homogeneous solution was cooled, diluted with aqueous $NaHCO_3$, and extracted (3×) with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Chromatographic purification (pentane–EtOAc, 1:1) gave orange crystals (0.173 g) of **37** (65% from **36**). An analytical sample had mp 222–224 °C (lit.[19] mp 221–223 °C, lit.[4b] mp 220–222 °C); IR (KBr) 1675, 1635, 1585 cm^{-1}; ^1H NMR δ 1.99 (t, J = 7 Hz, 2 H), 3.02 (t, J = 7 Hz, 2 H), 3.05 (s, 2 H), 4.05 (s, 4 H), 4.07 (s, 3 H), 7.34 (d, J = 8 Hz, 1 H), 7.48 (s, 1 H), 7.72 (t, J = 8 Hz, 1 H), 7.94 (d, J = 8 Hz, 1 H), 13.32 (s, 1 H); MS, *m/e* (relative intensity) 366 (M^+) (100), 294 (100), 279 (70), 262 (16), 234 (15). As described previously,[19] treatment of **37** with aqueous trifluoroacetic acid gave **38**, in 97% yield, mp 257–258 °C, with IR and ^1H NMR data in agreement with those reported:[19] MS, *m/e* (relative intensity) 322 (M^+) (100), 295 (92) 279 (96), 276 (36).

5β-Hydroxy-6,7,11-trimethoxy-1,2,3,4,4a,5,12,12aα-octahydro-2,5-naphthacenedione (36) and Conversion to 38. The hydrogenation of diols **29a,b** as described for **28a,b**, gave 95% of a crystalline mixture of epimeric triols (**35a,b**, R_f 0.2 and 0.4 in ethyl acetate–cyclohexane, 4:1), with the more polar epimer as the major component: ^1H NMR δ 1.52–3.36 (m, 10 H), 3.85 (s, 3 H), 3.89 (s, 3 H), 4.01 (s, 3 H), 4.42–4.85 (m, 1 H), 4.95 (br s, 2 H), 5.28 (br s, 1 H), 6.85 (d, J = 7 Hz, 1 H), 7.39–7.71 (m, 2 H). The triols were used without further purification or

characterization in the next oxidation step as follows. To a stirred solution of oxalyl chloride (0.2 mL, 2.2 mmol) in CH_2Cl_2 (5 mL) at −60 °C was added a solution of 0.34 mL of DMSO (4.4 mmol) and CH_2Cl_2 (1 mL). After the mixture was stirred for 3 min, a solution of triols **35a,b** (0.12 g, 0.32 mmol) in CH_2Cl_2 (5 mL) was added and stirring was continued for 15 min at −60 °C. The mixture was then cooled to −78 °C, and triethylamine (1.2 mL, 8.6 mmol) was added. After the mixture was stirred for 10 min, the cooling bath was removed, and after an additional 5 min, brine and $CHCl_3$ were added. Workup as shown for **34** and chromatography (pentane–ether, 1:1, and 5% CH_2Cl_2) gave 70 mg of **36** as white crystals (59%). An analytical sample had mp 164–165 °C ($CHCl_3$–hexane): IR (KBr) 1701, 1687, 1610, 1559 cm^{-1}; ^1H NMR δ 1.84–3.76 (m, 9 H), 3.84 (s, 3 H), 3.93 (s, 3 H), 4.01 (s, 3 H), 4.61 (s, OH), 6.89 (dd, J = 2, 6.5 Hz, 1 H), 7.43–7.70 (m, 2 H); MS, m/e (relative intensity) 370 (M^+) (100), 285 (16), 271 (18), 243 (42). The diketone **36** (80 mg, 0.26 mmol) was reacted with $Ag^{II}O$ and then with ethylene glycol as described for **34** to give 49 mg of **37** (71%), which was also converted to **38**, as shown above.

2-Acetyl-2,5-dihydroxy-7-methoxy-6,11-naphthacenedione (40). To a cooled (−78 °C) solution of (trimethylsilyl)acetylene (0.47 mL, 3.4 mmol) in THF (6 mL) was added *n*-butyllithium in hexane (2 mL, 2.8 mmol) under argon. After being stirred for 30 min at −78 °C, the above solution was added by syringe via septum to a reaction flask containing a stirred suspension of anhydrous cerium(III) chloride[25] (0.740 g, 3 mmol) in THF (8 mL), which was cooled to −78 °C, after being initially stirred overnight at room temperature. After further stirring for 30 min at −78 °C, a suspension of the ketone **38** (98 mg, 0.3 mmol) in THF (8 mL) was added via syringe and the resulting brown mixture was stirred at −78 °C for a further 6 h, then quenched with aqueous HCl, and extracted with EtOAc (3×). The combined organic layers were washed several times with brine, dried (Na_2SO_4), filtered, and evaporated in vacuo. A TLC test of the residue showed the presence of two colorless components of close polarity, which turned violet on standing. This mixture was purified by chromatography (pentane–ethyl acetate, 4:1) to give 75 mg of the first component and 53 mg of the second (**39a** and **39b**, total yield 82%). Elution with pentane–ethyl acetate, 1:1, gave 8 mg of recovered **38** (8%). The mixture of the two components was used directly for the next step, and chromatographic separation was effected for spectroscopic identification. The less polar component had mp 185–186 °C dec (benzene–hexane): IR (KBr) 1660, 1592 cm^{-1}; ^1H NMR δ 0.08 (s, 9 H), 0.12 (s, 9 H), 1.57 (br s, 1 H, OH), 2.14 (t, J = 7 Hz, 2 H), 3.02 (t, J = 7 Hz, 2 H), 3.20 (br s, 2 H), 4.09 (s, 3 H), 5.95 (s, 1 H, OH), 7.30–8.01 (m, 4 H), 8.43 (s, 1 H, OH); MS, m/e (relative intensity), 518 (M^+) (3), 500 (36), 482 (11), 427 (12), 251 (15). The second component had mp 172–174 °C dec (benzene–hexane): IR (KBr) 1662, 1593 cm^{-1}; ^1H NMR δ 0.06 (s, 9 H), 0.12 (s, 9 H), 2.01 (br, 1 H, OH), 2.13 (t, J = 7 Hz, 2 H), 3.03 (t, J = 7 Hz, 2 H), 3.16–3.21 (br, 2 H), 4.09 (s, 3 H), 5.95 (s, 1 H, OH), 7.30–8.02 (m, 4 H), 8.46 (s, 1 H, OH); MS, m/e (relative intensity) 500 (M^+ − 18) (40), 427 (5), 402 (12), 367 (10). To a solution of diastereomeric **39a,b** (0.103 g, 0.2 mmol) in THF (10 mL) were added HgO (50 mg), aqueous 9 N H_2SO_4 (2 mL), and water (4 mL), and the mixture was vigorously stirred at 70 °C for 2 h. After cooling, 10% aqueous HCl was added and the mixture was extracted with ethyl acetate. The organic layer was dried (Na_2SO_4), filtered, concentrated in vacuo, and purified by chromatography (benzene–ethyl acetate, 3:1) to give 42 mg of **40** (58%). An analytical sample had mp 208–210 °C (lit.[4f,h,p] mp 209–211 °C): IR (KBr) 3480, 1709, 1670, 1625 cm^{-1}; ^1H NMR δ 1.92–2.09 (m, 2 H), 2.37 (s, 3 H), 2.77 (d, J = 17 Hz, 1 H), 2.87–3.15 (m, 2 H), 3.30 (d, J = 17 Hz, 1 H), 3.79 (s, 1 H, OH), 4.07 (s, 3 H) 7.45 (s, 1 H), 7.73 (t, J = 8 Hz, 1 H), 7.92 (d, J = 8 Hz, 1 H), 13.37 (s, 1 H); MS, m/e (relative intensity) 366 (M^+) (12), 323 (100).

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An Asymmetric Synthesis of 5-*O*-Carbamoylpolyoxamic Acid from D-Serine

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A stereocontrolled and asymmetric synthesis of 5-*O*-carbamoylpolyoxamic acid (**2**), the major acyclic component of the polyoxin family of antifungal antibiotics, is reported. The sequence began with an erythro-selective addition of vinylmagnesium bromide to the oxazolidine aldehyde **6** (prepared from D-serine) to give the secondary allylic alcohols **7**/**8**. The derived urethane **12** underwent clean allylic rearrangement upon exposure to $PdCl_2(MeCN)_2$, yielding the primary allylic urethane **13**. Mild acidic methanolysis then gave the homoallylic alcohol **14**, which was shown to be configurationally pure by a Mosher ester analysis. Oxidation of **14** with $KMnO_4$ under CO_2-buffered conditions gave a mixture of lactols **19**/**20**. Further oxidation of these lactols with *N*-bromourea yielded a (2.5:1) mixture of γ-lactones **21** and **22** which was purified by chromatography and crystallization. Treatment of **21** with trifluoroacetic acid resulted in quantitative formation of lactone salt **23**, whereas hydrolysis of **21** with aqueous HCl gave **25** (=**2**·HCl) directly.

Introduction

The polyoxins are a family of important agricultural antibiotics isolated from *Streptomyces cacaoi* var. asoensis that exhibit marked and selective activity against phytopathogenic fungi.[1] They function by inhibiting chitin synthase, an enzyme which catalyzes the final step in the biosynthesis of chitin, a process necessary for proper cell wall assembly. Recent studies suggest that these compounds (or analogues thereof) may also be therapeutically useful against *Candida albicans*, a fungal pathogen which commonly affects humans.[2] There remains, however, the need for a more general synthetic approach to these and related peptidyl nucleoside antibiotics.[3,4]

(1) For a comprehensive review of the polyoxins, see: Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333 and references cited therein.

(2) Cf.: Shenbagamurthi, P.; Smith, H. A.; Becker, J. M.; Steinfeld, A.; Naider, F. *J. Med. Chem.* **1983**, *26*, 1518.

(3) Synthetic efforts directed toward the polyoxins include: (a) Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K. *J. Org. Chem.* **1986**, *51*, 5024. (b) Tabusa, F.; Yamada, T.; Suzuki, K.; Mukaiyama, T. *Chem. Lett.* **1984**, 405. (c) Kuzuhara, H.; Kimura, M.; Emoto, S. *Carbohydr. Res.* **1975**, *45*, 245. (d) Kuzuhara, H.; Ohrui, H.; Emoto, S. *Tetrahedron Lett.* **1973**, 5055. (e) Kuzuhara, H.; Emoto, S. *Ibid.* **1973**, 5051. (f) Ohrui, H.; Kuzuhara, H.; Emoto, S. *Ibid.* **1971**, 4267. (g) Ohdan, S.; Okamota, T.; Maeda, S.; Ichikawa, T.; Araki, Y.; Ishido, Y. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 981. (h) Damodaran, N. P.; Jones, G. H.; Moffatt, J. B. *J. Am. Chem. Soc.* **1971**, *93*, 3812.

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