A Convergent Approach toward the Tigliane Ring System

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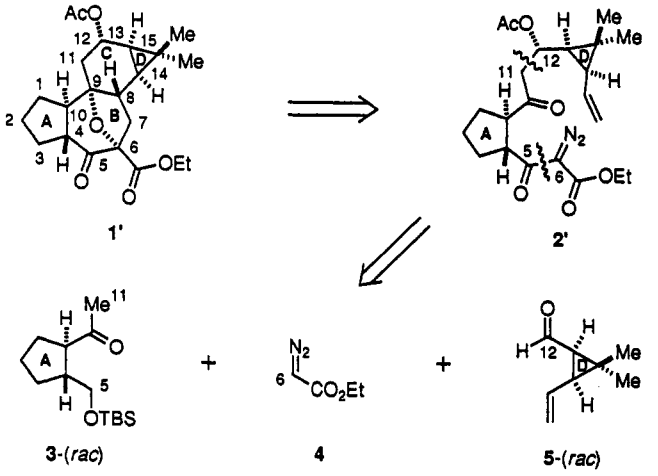
Summary: The C_6,C_9-oxido-bridged tigliane ring system was synthesized using a stereospecific rhodium(II)acetate-catalyzed tandem cyclization–cycloaddition reaction as the central step.

Diterpenes with a tigliane skeleton have played an important role in the development of a molecular mechanism for carcinogenesis.[1] The most recognized tumor promoters of this class of natural products are the 12,13-diesters of phorbol. To evaluate their structure–activity relationships, attention has been given to the preparation of modified derivatives.[2,3] In general, synthetic efforts have mainly resulted in the preparation of precursors to the natural material.[3,4] The studies of Wender have led to two different syntheses of phorbol itself.[5] His most recent approach is based on the formation of the B- and C-ring systems via an oxidopyrilium [5 + 2]-cycloaddition and subsequent introduction of the A- and D-rings.

We wish to report a different strategy to synthesize the C_6,C_9-oxido-bridged tigliane ring system 1 (Scheme I). The rhodium(II)-catalyzed formation of cyclic carbonyl ylides, when coupled to an intramolecular cycloaddition reaction[6] using precursor **2**, should allow for the formation of the B- and C-ring system in the presence of the A- and D-rings. Additionally, this one-pot double ring closure could fix not only the natural occurring stereochemistry between the newly formed chiral centers at C-8 and C-9 but at the same time could relate them in the correct stereochemistry to the chiral centers at C-4, C-10, C-13, and C-14. This convergent strategy connects building blocks **3** and **5**, containing the A- and D-carbocycles, via an aldol reaction.

Scheme I



Subsequent acetylation of the newly formed alcohol and attachment of **4** to yield the α-diazo β-keto ester would then provide cyclization precursor **2'**. To evaluate this projected synthetic plan, model compound **10** (Scheme II) was prepared to investigate the stability of the cyclopropane structure under the ring-closure conditions and its stereochemical influence on the formation of the B/C ring juncture. Second, the oxido-bridged tigliane system was prepared to evaluate the use of the cyclopentane ring in the overall ring closure process.

To obtain the D-ring portion **5**, ethyl chrysanthemate was converted to *cis*-2,2-dimethyl-3-vinylcyclopropanecarboxylic acid (**6**)[7] (Scheme II). The acid was reduced with lithium aluminum hydride, and the resulting alcohol was oxidized (Swern oxidation) to yield the highly volatile aldehyde **5** (85% for two steps). TBS-protected 5-hydroxy-2-pentanone was coupled with aldehyde **5**, and the resulting aldol product was obtained (49%). The product was a 3.2:1.0 mixture with the major isomer **7** possessing the unnatural 12(*S**)-hydroxy configuration. This 12(*S**)-hydroxy isomer is that predicted by the Felkin–Ahn rule for the aldol reaction of the chiral aldehyde **5**. The diastereomers were separated by HPLC. The major isomer **7** was acetylated, the terminal protected primary alcohol was desilylated with hydrogen fluoride, and the alcohol was oxidized to aldehyde **8** (49% overall yield). A tin(II) chloride catalyzed condensation with ethyl diazoacetate gave the β-keto ester (76%).[8] Diazo transfer[9] to the activated methylene group of the β-keto ester gave the α-diazo derivative **9** (58%), possessing all the necessary functionalities required for the crucial cyclization step. Reaction of the diazo derivative **9** with rhodium(II) acetate in boiling toluene[6] gave crystalline **10** (mp 115 °C) as the

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(3) Shigeno, K.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 4937.

(4) (a) Rigby, J. H. In *Studies in Natural Products Chemistry*; Atta-ur Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, p 233. (b) Magar, S. S.; Desai, R. C.; Fuchs, P. L. *J. Org. Chem.* **1992**, *57*, 5360. (c) Bulman Page, P. C.; Jennens, D. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2587. Corrected: *Ibid.* **1993**, 877. (d) Harwood, L. M.; Ishikawa, T.; Phillips, H.; Watkin, D. *J. Chem. Soc., Chem. Commun.* **1991**, 527. (e) McLoughlin, J. I.; Brahma, R.; Campopiano, O.; Little, R. D. *Tetrahedron Lett.* **1990**, *31*, 1377. (f) Rigby, J. H.; Kierkus, P. C.; Head, D. *Tetrahedron Lett.* **1989**, *30*, 5073 and references cited therein.

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(6) For recent reviews and lead references see: (a) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385. (b) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100. (c) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28.

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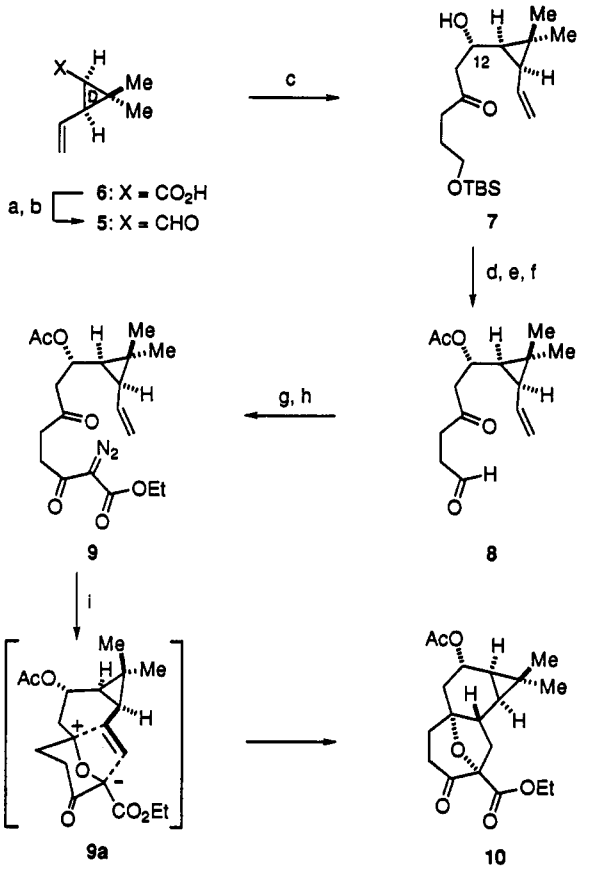
Scheme II[a]

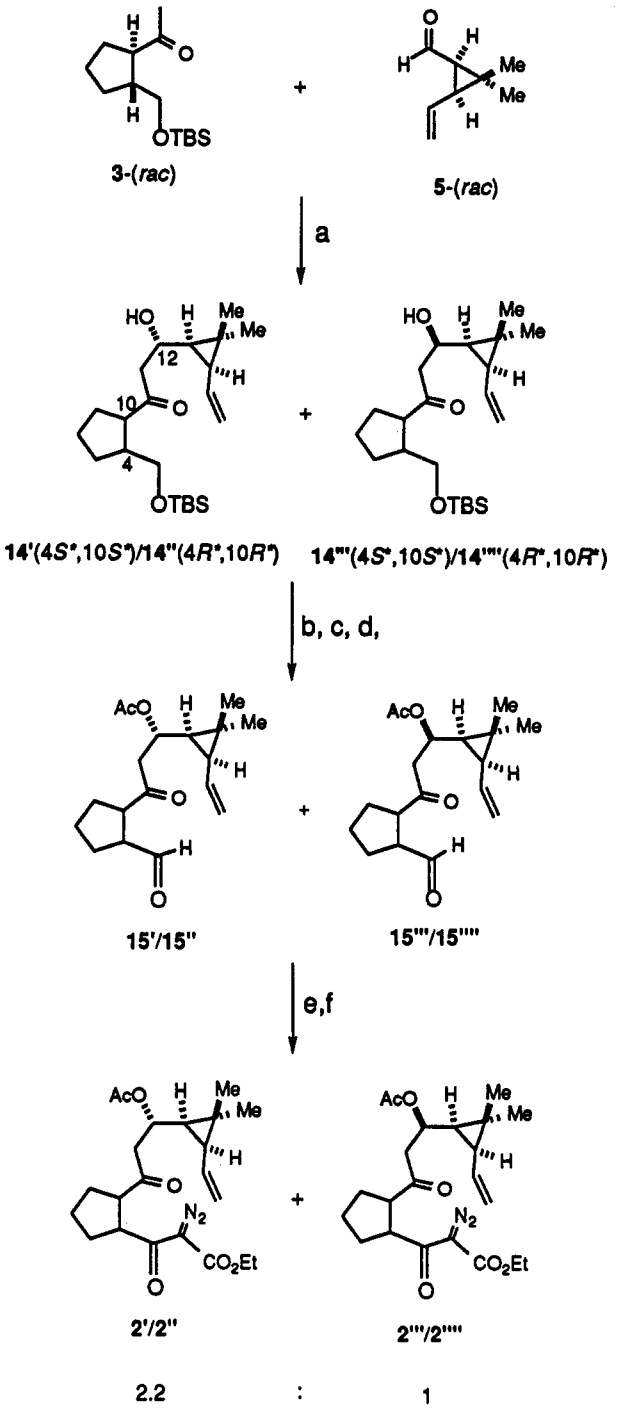


[a] Key: (a) $LiAlH_4$, ether, rt, 20 h; (b) DMSO/$(COCl)_2$, CH_2Cl_2, −78 °C, 35 min, then Et_3N; (c) $CH_3CO(CH_2)_3OTBS$, LDA, THF, −78 °C, 16 h; (d) Ac_2O/4-DMAP/pyridine, rt, 17 h; (e) 48% HF, CH_3CN, 0 °C, 22 h; (f) PCC/Al_2O_3, CH_2Cl_2, 3 h; (g) 4, $SnCl_2$, CH_2Cl_2, 14 h; (h) MsN_3, CH_3CN, Et_3N, rt, 23 h; (i) $Rh_2(OAc)_4$, toluene, 100 °C, 1 h.

only product (72% yield). The stereochemistry of the oxido-bridged tricyclic **10** was assigned on the basis of single-crystal X-ray analysis. The crystallization also was carried out with the minor, natural 12(*R**)-isomer of the aldol reaction. The structure and stereochemistry of the ring-closed product (75% yield), excluding the C-12 hydroxyl function, was identical to that of compound **10**, as shown by extensive NOE proton studies with both hydroxy isomers. The finding of the identical ring stereochemistry of this ring-closed product of both isomeric acetate esters indicated that this configuration of the acetoxy group at C-12 does not have a role in the steric result of the ring-closure reaction.

With these results in hand, a synthesis of the A-ring subunit **3** was developed. The conjugate addition of 1-(ethylsulfinyl)-1-(ethylthio)ethane to 1-carbethoxycyclopentene (**11**)[10] and subsequent cleavage of the thiosulfoxide group with 60% perchloric acid[11] afforded, exclusively, *trans*-**12**. Reduction with lithium aluminum hydride[12] and silylation of the primary alcohol yielded **13**, and Swern oxidation produced **3** (37% over three steps).

Scheme III[a]



[a] Key: (a) LDA, THF, −78 °C, overnight; (b) Ac_2O/4-DMAP/pyridine, rt, overnight; (c) 48% HF, CH_3CN, 0 °C, 10 min; (d) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N; (e) 4, $SnCl_2$, CH_2Cl_2, 3 h; (f) MsN_3, CH_3CN, Et_3N, rt, 24 h.

The next step in our strategy was the aldol reaction between **3** and **5** (Scheme III). This reaction proceeded in 81% yield and, similar to the model reaction, gave a 2.2:1.0 mixture of aldol adducts 14'/14'' and its 12(*R**)-hydroxy isomers.[13] Following the synthetic steps used for the model compound **7**, the inseparable isomeric mixture

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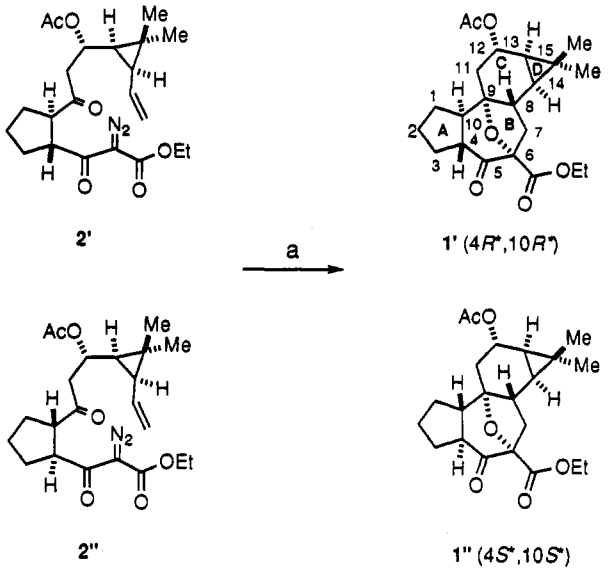
(12) All trials to reduce the carboxy function in the presence of the sulfur groups only led to unsatisfactory results.

(13) Additionally, the aldol reaction yields a 1:1 enantiomeric mixture of two diastereomeric aldols, each containing a different one of both possible *trans*-A-ring pieces, since the A- and D-ring synthons were used in racemic form. However, to simplify the structure of the formulas in Scheme II, only the isomer with the stereochemistry of targeted **1** is drawn and the relations are mentioned in the text.

Scheme IV[a]



[a] Key: (a) $Rh_2(OAc)_4$, toluene, 100 °C, 1 h.

of 14 was acetylated and the primary hydroxyl groups were deprotected and subsequently oxidized to the aldehydes **15**. Their condensation with ethyl diazoacetate,[8] followed by the diazo transfer reaction,[9] gave a diastereomeric mixture which was separated by flash chromatography into **2'/2"** (12*S**) and its **2'''/2''''** (12*R**) isomer (ratio 2.2:1.0), and the combined yield was 61%.

In the final step (Scheme IV), the carbonyl ylide, generated *in situ* from the major isomer **2'/2"** in the presence of a catalytic amount of Rh(II)acetate, underwent an intramolecular addition with the olefin to form the C_6,C_9-oxido-bridged tigliane ring system. Equal amounts of two products were isolated, by column chromatography, in a total amount of 86%. The structures of the two crystalline product were determined by single-crystal X-ray analysis. The higher melting product (mp 195 °C) was found to be **1'** (4*R**,10*R**) and the lower melting product (mp 121 °C) was **1"** (4*S**,10*S**), the expected result since racemic **3** was used in the aldol reaction. The minor isomeric mixture **2'''/2''''** (12*R**) gave similar results upon ring closure.

Summary. In all the rhodium-promoted ring closures investigated in this study, the two new stereocenters at C-8 and C-9 were formed with the correct configurations relative to C-14 and C-15 possessed in the natural tigliane compounds. This result is independent of *trans*-configuration at the asymmetric centers at C-4 and C-10.[14,15] Also, the configuration of the 12-hydroxy group plays no role in the steric outcome of the B- and C-ring closures. The high stereospecificity in the ring-closure reaction could be related to steric interactions and/or the introduction of conformational strain in the tether which does not favor a transition state that leads the cyclopropane ring and the oxido-bridge to be on the same side of the molecule.

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Supplementary Material Available: Experimental details, spectral data, molecular mechanics calculations results, and the ORTEP information of the X-ray structure determination (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) MM2 calculations of all possible end-products, however, favored the product with the opposite configuration at C-6, C-8, and C-9 in the case of the 4*S**,10*S**-isomer; details are presented in the supplementary material.

(15) The enantiomerically pure synthesis of A-ring synthons of tiglianes which could be used for our approach was investigated by: Becicka, B. T.; Koerwitz, F. L.; Drtina, G. J.; Baenzinger, N. C.; Wiemer, D. F. *J. Org. Chem.* **1990**, *55*, 5613.