ORGANIC LETTERS

2008
Vol. 10, No. 13
2833−2836

Synthesis of an Advanced Intermediate for (+)-Pillaromycinone. Staunton−Weinreb Annulation Revisited

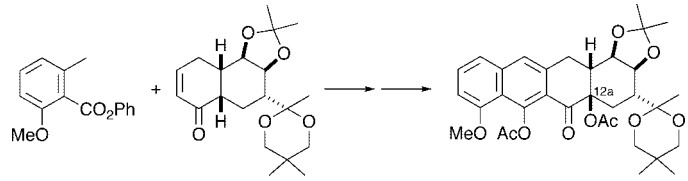
James D. White,* F. W. J. Demnitz, Qing Xu, and William H. C. Martin

Department of Chemistry, Oregon State University, Corvallis, Oregon 97331

james.white@oregonstate.edu

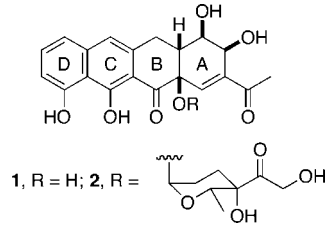
Received April 28, 2008

ABSTRACT



Condensation of an orsellinate anion with a 2-cyclohexenone (Staunton−Weinreb annulation) afforded a linear tetracycle which was converted to a protected derivative of 12a-epipillaromycinone. Methodology for introducing a 12a-hydroxyl substituent into the tetracycle with correct (*R*) configuration is described.

(+)-Pillaromycinone (**1**)[1] is the aglycone of the anthracycline antibiotic (−)-pillaromycin A (**2**), a substance isolated from the culture broth of *Streptomyces flavovireus*.[2] Pillaromycin A displays significant antitumor activity and is reported to be less cardiotoxic than other members of the anthracycline family used medicinally.[3] (+)-Pillaromycinone (**1**), along with the unusual sugar pillarose, is obtained from **2** by mild acidic hydrolysis.[2]



Our earlier approach to the synthesis of **1** employed condensation of an orsellinate anion with a β-methoxy α,β-unsaturated ketone to generate the C-ring of the tetracycle.[4,5]

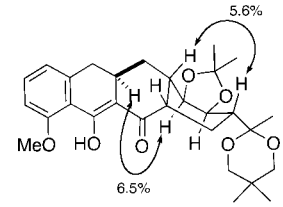


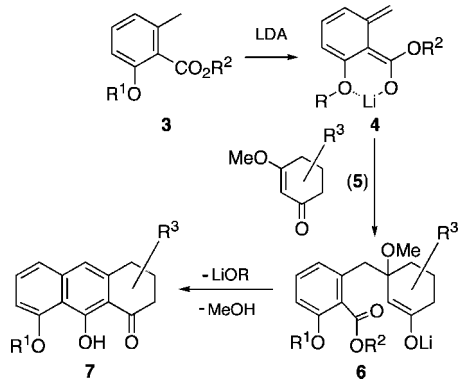
Figure 1. Conformation of **24** deduced from NOE measurements.

This annulation is patterned on a reaction discovered independently by Staunton[6] and Weinreb[7] in the course of their studies on the synthesis of polyketide natural products and is represented generically in Scheme 1. A requirement for the Staunton−Weinreb annulation to proceed successfully

(1) Asai, M. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 1706.
(2) Asai, M. *Chem. Pharm. Bull. (Tokyo)* **1970**, *18*, 1699.
(3) Shibata, M.; Asai, M.; Mizuno, K.; Miyake, A.; Tatsuoka, S. *Proc. Jpn. Acad.* **1964**, *40*, 296.
(4) White, J. D.; Nolen, E. G., Jr.; Miller, C. H. *J. Org. Chem.* **1986**, *51*, 1150.
(5) For other approaches to the synthesis of pillaromycinone, see: (a) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252. (b) Majuwdar, G.; Pal, R.; Murphy, K.V.S.N.; Mal, D. *J. Chem. Soc., Perkins Trans.* **1994**, 309. (c) Wang, L.; Meegalla, S. K.; Fang, C.-L.; Rodrigo, I. *Can. J. Chem.* **2002**, *80*, 728.
(6) Staunton, J.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1053.
(7) Dodd, J. H.; Starrett, J. E.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 1811.

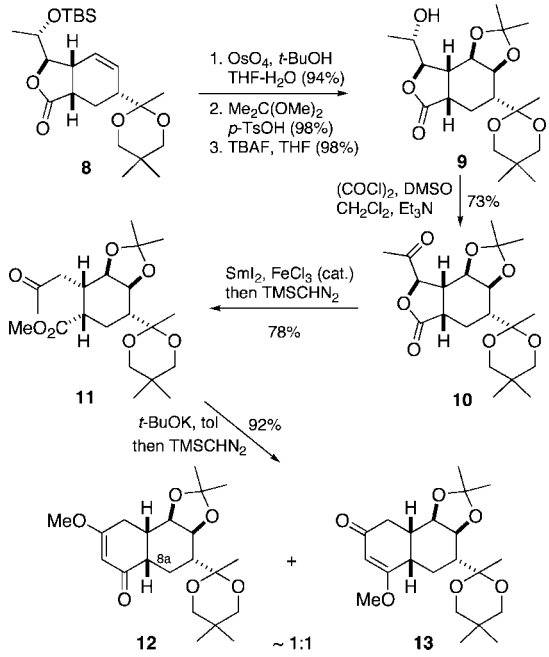
10.1021/ol8009732 CCC: $40.75
Published on Web 06/07/2008

Scheme 1. Staunton−Weinreb Annulation



is the presence of an alkoxy substituent ortho to the ester in **3**, implying that a chelate species **4** is involved in the reaction with enone **5**. The sequence of steps following formation of enolate **6** which leads to **7** is uncertain, but the basic properties of an intermediate such as **4** or **6** have consequences if there is a stereogenic center in **5** that can be epimerized. This concern prompted us to reexamine our earlier approach to **1** which featured a Staunton−Weinreb assembly of its tetracyclic nucleus,[4] but which subsequent studies found to be difficult to reproduce.

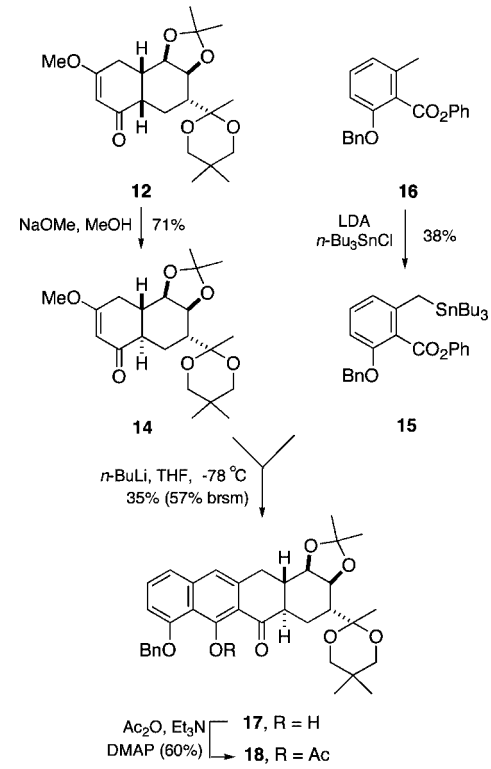
Scheme 2. Synthesis of Methoxy Enones **12** and **13**



Osmylation of previously synthesized **8**[8] occurred exclusively from the exo face of the cyclohexene double bond,

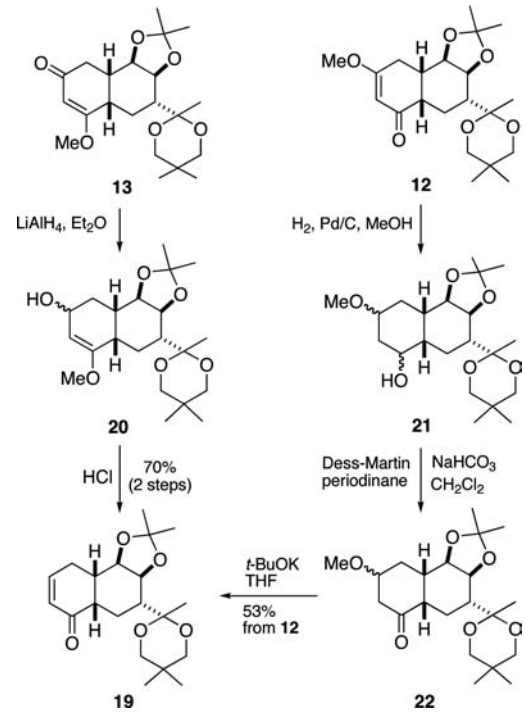
(8) White, J. D.; Demnitz, F. W. J.; Oda, H.; Hassler, C.; Snyder, J. P. *Org. Lett.* **2000**, *2*, 3313.

Scheme 3. Staunton−Weinreb Annulation with **14**

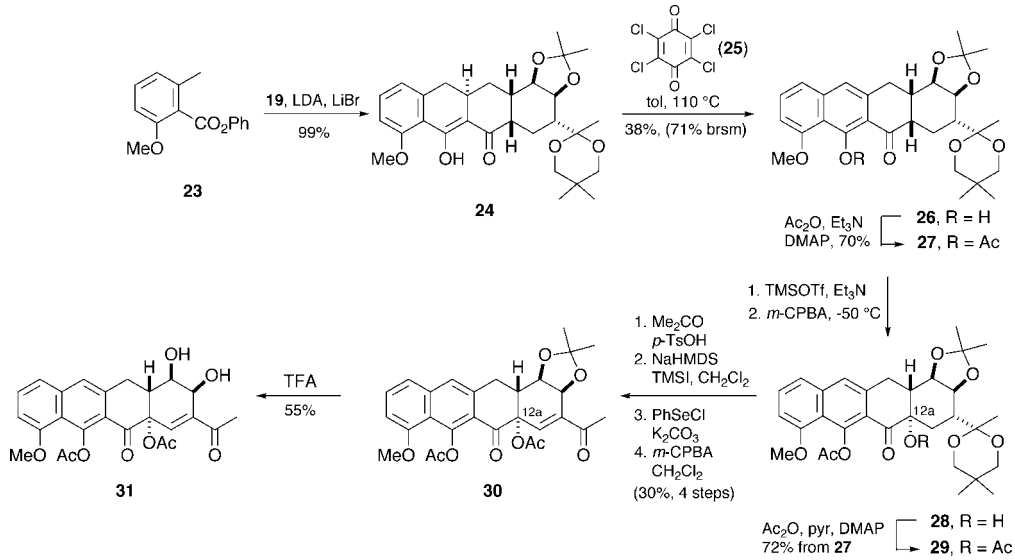


and the resulting *cis*-diol was protected as its acetonide (Scheme 2). Cleavage of the TBS ether then gave hydroxy

Scheme 4. Convergence of β-Methoxy Enones **12** and **13** Upon Enone **19**

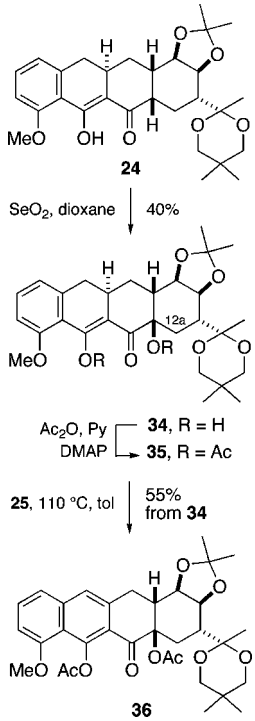


Scheme 5. Staunton−Weinreb Annulation Leading to Protected 12a-Epipillaromycinone **31**



lactone **9**. Swern oxidation of **9** to ketone **10** was followed by reductive scission of the lactone[9] to give a keto acid which was methylated to furnish keto ester **11**. Intramolecular Claisen condensation[10] of **11** yielded an unstable enolic β-diketone which upon methylation produced β-methoxy enones **12** and **13** in a 1:1 ratio.

Scheme 6. Introduction of a (12a*R*)-Hydroxyl Substituent



A previously successful condensation of orsellinate **3** (R^1 = Me, R^2 = Ph) with an enone similar to **12**[4] led us to expect successful annulation with **12** itself. In fact, no tetracycle was formed in this reaction, and apart from self-condensation of **3**, the only change was deprotonation at the ring fusion of **12**. This prompted the speculation that the trans-fused isomer of **12** could behave differently in its condensation with orsellinate anion **4**, and accordingly, **12** was isomerized with sodium methoxide to produce *trans*-decalone **14** in a 2.6:1 mixture with **12** that was easily separated (Scheme 3).

Before investing **14** in a Staunton−Weinreb annulation, we decided to prepare the lithio orsellinate **4** via transmetalation of **15** in the hope that this would minimize self-condensation of the latter. For this reason, **16** in which the methyl ether is replaced by a benzyl ether[11] was converted to stannane **15**. Treatment of **15** with *n*-butyllithium under carefully controlled conditions followed by addition of **14** led to highly fluorescent ketone **17**, albeit in modest yield. Acetylation of **17** required forcing conditions due to steric hindrance around the naphthol peri position but gave nonfluorescent acetate **18** in serviceable yield. The foregoing results inform us that successful Staunton−Weinreb annulation requires the absence of protons in the enone partner that can be removed by anion **4**. The failure of **12** to undergo annulation, in contrast to **14**, can be attributed to the greater acidity of the C8a hydrogen in the cis-fused isomer, thus preventing Michael addition by anion **4**.

It is well-known that Michael addition to cyclohex-2-enone is faster than conjugate addition to its 3-methoxy substituted analogue,[12] and it was therefore of interest to determine whether more efficient annulation could be achieved with enone **19** (Scheme 4). This raised the attractive prospect that

(9) Girard, P.; Nancy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(10) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 4597.

(11) Studies with naturally derived *O*-methylpillaromycinone confirmed that cleavage of the methyl ether to return **1** was difficult.

(12) Jung, M. E. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol *4*, pp 1−67..

both methoxy enones **12** and **13** could be used to obtain **19**. First, **13** was reduced to alcohol **20**, which upon acidic hydrolysis led directly to **19**. The same enone was obtained from **12** after catalytic hydrogenation, which yielded a mixture of alcohol **21** and ketone **22**, followed by oxidation of the mixture and base-catalyzed elimination.

Condensation of the lithio anion of **23** with **19** in the presence of lithium bromide proceeded in excellent yield to give tetracycle **24** as a mixture of keto−enol tautomers (Scheme 5). Aromatization of ring C of **24** proved surprisingly difficult, the only reagent able to accomplish this dehydrogenation being *p*-chloranil (**25**) in toluene at elevated temperature.[13] The phenolic hydroxyl group of **26** was acetylated before ketone **27** was converted to its silyl enol ether. Epoxidation followed by acetylation of the resultant α-hydroxy ketone then afforded diacetoxy ketone **29**. Unfortunately, the acetate at C12a of **29** was subsequently found to have the undesired (*S*) configuration, rather than (*R*) stereochemistry required for **1**. Treatment of **29** with *p*-toluenesulfonic acid in acetone yielded a methyl ketone which was converted to α,*β*-unsaturated ketone **30**[14] via selenylation and oxidation. Final cleavage of the acetonide from **30** produced diol **31**.

Installation of a hydroxyl substituent at C12a with the correct (*R*) configuration became possible when it was recognized from an NMR study that the conformation of **24** differed significantly from its aromatized counterpart **26**. Specifically, ring A of **24** was found to exist in a boat conformation with the ketone of ring B oriented axially (Figure 1). This finding led to the prediction that oxidation at C12a of **24** would occur from the *β* face and, in fact, exposure of **24** to selenium dioxide produced **32** as the sole stereoisomer (Scheme 6). Acetylation of **32** followed by aromatization of diacetate **33** with *p*-chloranil (**25**) afforded **34** which was shown to be epimeric with **29**.

In summary, tetracyclic structures containing the functionality and stereochemistry of pillaromycinone (**1**) have been prepared using Staunton−Weinreb annulation as a key step. Further progress toward **1** and pillaromycin A (**2**) is predicated upon advancing **34** along lines employed in the conversion of **29** to **31**.

Acknowledgment. We are grateful to Dr. Juris Fotins for assistance with the preparation of **19** and to Dr. Yukimasa Hidefumi, Takeda Chemical Industries, for a sample of natural pillaromycin A. This research was supported by the National Science Foundation through grants 0076103-CHE and 0413994-CHE.

Supporting Information Available: Experimental procedures and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8009732

(13) This reaction showed the characteristics of product inhibition, proceeding cleanly to ca. 30% completion but then terminating, apparently due to complex formation between **24** and the hydroquinone byproduct from **25**. Unoxidized **24**, which is easily distinguishable from highly fluorescent **26**, was recovered and recycled.

(14) In work to be described in a future publication, pillaromycinone (**1**), obtained by hydrolysis of natural pillaromycin A (**2**), was converted in five steps to the C12a epimer of **30**. The ^{1}H and ^{13}C NMR spectra of **30** did not match those of the compound derived from **1**, and it was apparent from the chemical shift of the C4a proton that the AB rings of **30** were transfused.