ORGANIC LETTERS

2001
Vol. 3, No. 1
115−117

Facile Entry to the Tetracyclic 5-7-6-3 Tigliane Ring System

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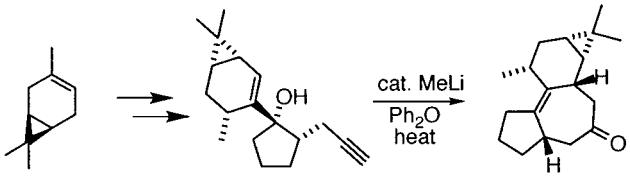
Received November 3, 2000

ABSTRACT



A tandem anionic 5-exo-dig cyclization/Claisen rearrangement sequence was used to effect a facile, "one-pot" conversion of an appropriately substituted 4-alkyn-1-ol to the tetracyclic carbon core structure of phorbol. The synthesis was conducted using readily available nonracemic starting materials to provide the target structure as a single enantiomer in high chemical yield.

Among the most powerful methods of ring construction are the various cascade reactions that allow several synthetic transformations to take place in a single reaction vessel. Applications of these sequential processes have resulted in many elegant synthetic approaches to natural products, including morphine,[1] the prostaglandins,[2] $\Delta^{9(12)}$capnellene,[3] the scopadulcic acids,[4] and dynemycin A,[5] to mention a few examples.

We have recently reported the use of a tandem anionic cyclization/Claisen rearrangement sequence as a convenient and highly stereoselective route to tricyclic ring systems.[6] These reactions involve the use of appropriately substituted 4-alkyn-1-ols, which are easily converted to the target ring structures in high yield simply on heating and in the presence of catalytic amounts of a strong base.[7] We have now explored this strategy as an efficient route to the tetracyclic tigliane core found in a number of biologically active compounds such as phorbol, a potent tumor promoter.[8]

Synthetic approaches to the tigliane ring system have been previously described by Wender,[9] Paquette,[10] Shibasaki,[11] Dauben,[12] and others.[13] Wender reported the first synthesis of the phorbol skeleton in 1987[9a] and of phorbol itself a few years later.[9b] His efforts culminated in the elegant asymmetric total synthesis of phorbol in 1997.[9e] Key to this strategy is the formation of the B/C ring fragment through an intramolecular oxidopyrilium−alkene [5 + 2] cycloaddition reaction (Scheme 1).[9e]

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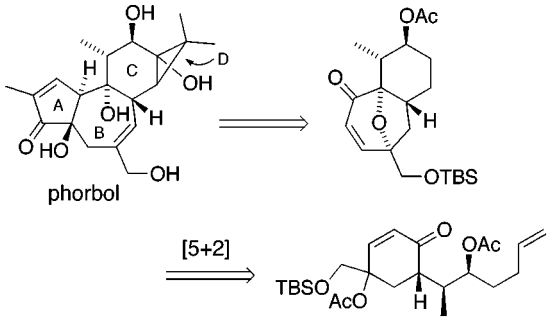
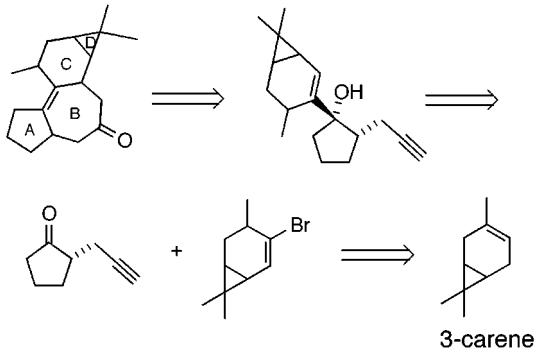
10.1021/ol006823a CCC: $20.00
Published on Web 12/15/2000

Scheme 1



Our approach to the tigliane skeleton, shown retrosynthetically in Scheme 2, is highly convergent, focusing initially

Scheme 2

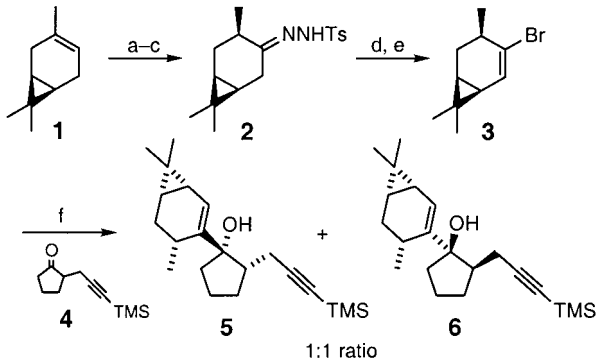


on the separate preparation of the A and C/D ring fragments, which are then coupled in the final stages of the synthesis to provide the requisite acetylenic alcohol precursor. The necessary C/D fragment was prepared in a straightforward fashion as reported earlier by Paquette et al.,[14] using commercially available (+)-3-carene as the starting material. In our hands, this five-step sequence produced the bicyclic vinylbromide **3** in 57% overall yield, the key step being the Shapiro reaction[15] involving tosylhydrazone **2** (Scheme 3).

Treatment of the vinyl bromide **3** with *t*-BuLi, followed by addition of anhydrous $CeCl_3$, and reaction of the resulting vinyl cerate with (±)-2-(3-trimethylsilyl-2-propynyl)cyclopentanone produced a 1:1 mixture of the diastereomeric acetylenic alcohols **5** and **6** in 79% yield.

The formation of diastereomers in this case is unavoidable, resulting from the reaction of a nonracemic vinylcerium derivative, ultimately derived from (+)-3-carene, with a racemic ketone (**4**). However, it appears that the coupling process itself is highly Cram-diastereoselective, allowing delivery of the vinylcerium nucleophile from the less hindered face of the ketone almost exclusively. This mode of addition establishes the desired *cis* relationship between the hydroxyl and acetylenic moieties in **5** and **6**; in fact, only trace amounts of the corresponding *trans* isomers were detected in the product mixture. Unlike the modest degree

Scheme 3

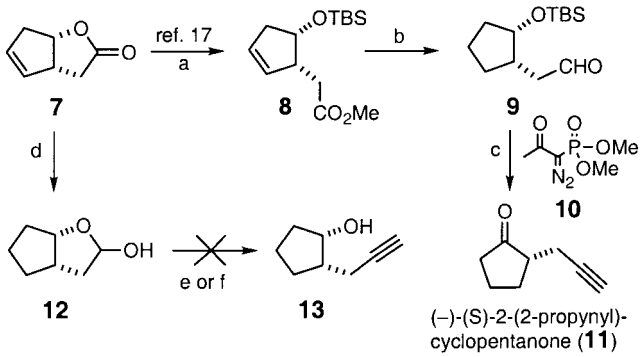


Conditions and yields: (a) BF_3•Et_2O/ $NaBH_4$ then H_2O_2/HO^-; (b) Jones oxidation; (c) H_2NNHTs (82% from **1**); (d) *n*-BuLi/TMEDA –60°C then warm to RT; (e) $BrCF_2CF_2Br$, –60 °C (70%); (f) i. *t*-BuLi/THF, –78 °C, ii. $CeCl_3$/THF, iii. **4** (79%)

of diastereoselectivity (~5:1 *cis*:*trans*) observed in our published model studies involving simple 1-cyclohexenylcerates,[6] the excellent selectivity observed here is undoubtedly due to the increased steric demand imposed by the bulky bicyclic nucleophile.

Our original plan was to separate the diastereomeric alcohols **5** and **6** and use these products individually for the tandem cyclization/Claisen rearrangement reaction; however, all attempts to separate the two isomers were unsuccessful. To avoid this problem altogether, it was decided to synthesize the requisite cyclopentanone derivative in an enantiomerically pure form using commercially available nonracemic lactone,[16,17] (1*S*,5*R*)-(−)-oxabicyclo[3.3.0]oct-6-en-3-one, as the starting material. As shown in Scheme 4, this sequence

Scheme 4



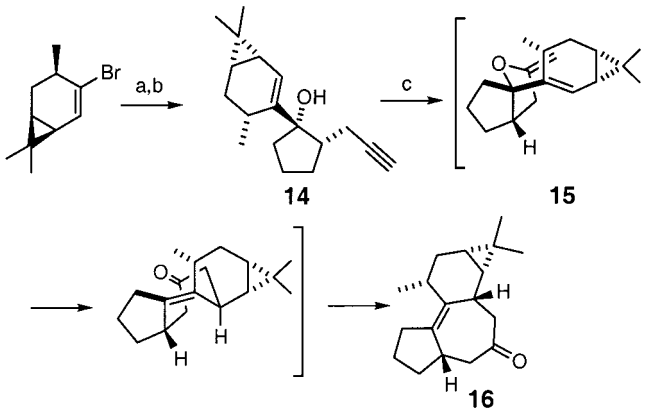
Conditions and yields: (a) TBSCl, Et_3N, DMAP; (b) i. H_2/Pd/C; ii. DIBAL (91% 2 steps); (c) i. **10**, K_2CO_3/MeOH (88%); ii. TBAF/THF; iii. $(COCl)_2$/DMSO, –78 °C, DCM, Et_3N (76% 2 steps); (d) i. H_2/Pd/C; ii. DIBAL (89% 2 steps); e) **10**, K_2CO_3/MeOH; f) $Me_3SiC(N_2)Li$

involves the initial preparation of the TBS-protected hydroxy ester **8**, followed by catalytic hydrogenation and DIBAL reduction to provide aldehyde **9**. On treatment with dimethyl (1-diazo-2-oxopropyl)phosphonate **10** and K_2CO_3 in metha-

nol,[18] **9** was efficiently converted to the corresponding alkyne derivative. Subsequent removal of the TBS moiety and Swern oxidation were used to complete the synthesis of nonracemic (*S*)-(−)-2-(2-propynyl)cyclopentanone **11**. It should be noted that all attempts to convert lactol **12** directly to the 2-propargylcyclopentanol **13** using either dimethyl (1-diazo-2-oxopropyl)phosphonate[19] or lithium TMS-diazomethane[20] failed completely and, as a result, the slightly longer route outlined above, was employed.

With (−)-**11** at hand, the synthesis of homochiral alkynol **14** was achieved in a straightforward fashion, following essentially the protocol described above for the preparation of **5** and **6** (Scheme 5). Consistent with our previous results

Scheme 5



Conditions and yields: (a) i. *t*-BuLi, –78 °C; ii. $CeCl_3$/THF, –78 °C; (b) i. **11**; ii. NH_4Cl (82%); (c) 10 mol% MeLi, Ph_2O, 185 °C, 1 h (76%)

employing less complex systems,[6] **14** was subsequently converted to the fused 5-7-6-3 ring system under our usual conditions for the tandem 5-exo-dig cyclization/Claisen rearrangement. Thus, on exposure to catalytic MeLi and heat for a period of just 1 h, **14** was readily converted to **16** as a single stereoisomer in 76% isolated yield after chromatography.

The ^1H and ^{13}C spectra of **16** are in full agreement with the assigned structure. The proton and carbon chemical shifts were secured by a combination of NMR experiments (gradient COSY, gradient HMQC, gradient HMBC, and DEPT-135) and the ring stereochemistry was confirmed by 1D NOE difference experiments. As shown in Figure 1, significant nuclear Overhauser enhancements were observed for H_c-H_e and H_c-H_d, and a small but observable (0.7%)

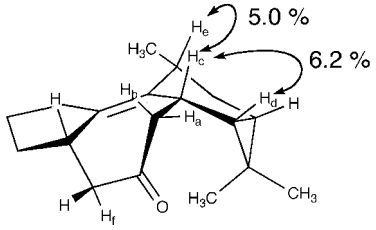


Figure 1. Diagnostic nuclear Overhauser enhancements in **16**.

enhancement was also detected between H_f and the more downshifted methyl group protons on the cyclopropyl ring. Molecular modeling experiments[21] performed on this compound reveal a puckered overall ring conformation that allows this methyl group to be relatively proximate to proton H_f, accounting for the small enhancement. It is also of interest to note that the chemical shifts of protons a and b (Figure 1), as well as the relevant coupling constants (J_{ac}, J_{bc}, J_{cd}), are very close to those found in analogous, previously synthesized tricyclic ring systems.[6]

The exclusive formation of **16** as a single stereoisomer is in accord with our earlier observations involving similar systems,[6] suggesting a chairlike transition state (**15**, Scheme 4) for the Claisen rearrangement. As a result of the *cis* relationship between the cyclopropyl and methyl groups in the bicyclic vinyl bromide **3**, the stereochemistry of the final C/D ring fragment in the tetracyclic product is opposite to that found in the naturally occurring phorboids. Nevertheless, the facile formation of the tetracycle **16** through the tandem cyclization/Claisen rearrangement process is a significant preliminary finding and clearly demonstrates the feasibility of the sequence at hand as a novel and extremely straightforward route to the fused 5-7-6-3 ring system.

Acknowledgment. This work was supported by grants from the donors of the Petroleum Research Fund, administered by the American Chemical Society, the Research Corporation (Cottrell College Science Award), and the National Institutes of Health (GM60972-01). S.E.R. and M.A.F. acknowledge Pfizer, Inc., for Summer Fellowships (Pfizer Summer Undergraduate Fellowship and PREPARE programs). We are also grateful to Dr. Walt Massefski of Pfizer Central Research, Groton, CT, for performing a complete NMR analysis of compound **16**.

Supporting Information Available: Detailed experimental procedures with spectroscopic data for compounds **8**, **9**, **11**, **13**, **14** and **16**, as well as the intermediate products in Scheme 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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