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Total Synthesis of (+)-α-Onocerin in Four Steps via Four-Component Coupling and Tetracyclization Steps

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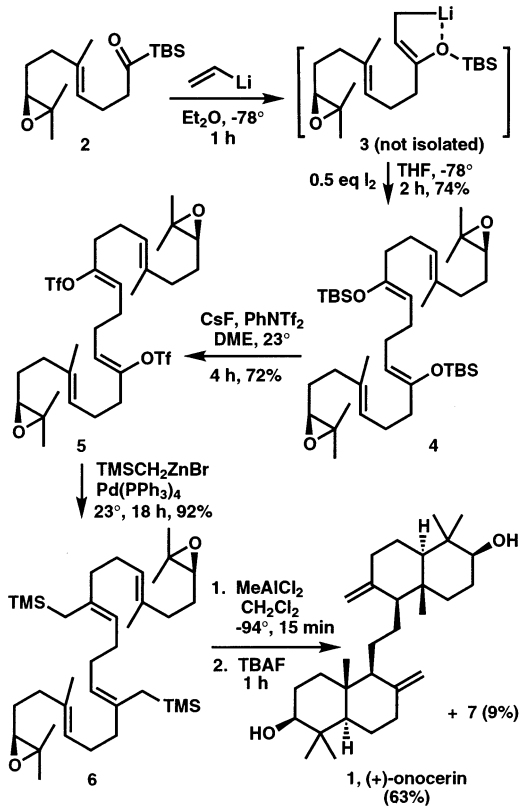
We describe herein an exceedingly short and effective enantioselective total synthesis of (+)-α-onocerin (**1**)[1] using novel synthetic methodology. A previous synthesis of this substance, by Stork and co-workers in 1963,[2] relied on numerous steps, conventional resolution of an advanced racemic intermediate, and coupling methodology demonstrated earlier (1957) by one of us for the synthesis of the chiral parent hydrocarbon, α-onoceradiene.[3] The present synthetic plan is based on new or recently developed reaction methodology, including (1) site-selective and enantioselective terminal epoxidation of farnesyl acetate;[4,5] (2) stereospecific synthesis of *tert*-butyldimethylsilyl (TBS) vinyl ethers from acyl silanes by nucleophilic addition to carbonyl, Brook rearrangement, and alkylation;[6] (3) one-flask, four-component coupling involving oxidative dimerization; (4) direct and facile conversion of vinyl TBS ethers to vinyl triflates and allylic silanes; and (5) efficient tetracyclization of a bis-allylic silane. Our results also show that biomimetic, epoxide-initiated cation−olefin cyclization to terpenic decalin systems can proceed not only by the commonly accepted chair−chair transition state (plant tetracyclic triterpene A/B folding) but also to an appreciable extent by a chair−boat pathway (steroid A/B folding).[7]

The four-step synthesis of (+)-α-onocerin (**1**) is outlined in Scheme 1. Chiral epoxy ketone **2**, synthesized enantioselectively as previously described,[4−6] was treated with 1.1 equiv of vinyllithium in Et_2O at −78 °C, and after 1 h a solution of 0.5 equiv of I_2 in THF was added slowly. After a reaction time of 2 h at −78 °C, extractive workup and column chromatography on silica gel (sg) afforded diepoxide **4** stereoselectively and in 74% yield. This remarkable one-flask, four-component coupling process occurs via the chelated *Z*-allylic lithium reagent **3**, which is formed from **2** by a carbonyl addition and Brook rearrangement sequence.[6] Copper(II) pivalate can be used in lieu of I_2 for the generation of **4** from **3**. The bis-vinyl TBS ether **4** was transformed directly into the corresponding bis-vinyl triflate **5** in 72% yield by a very useful new method consisting of simply stirring the TBS ether with an excess of vacuum-dried (300 °C) CsF and dry *N*-phenyltrifluoromethanesulfonimide in dry dimethoxyethane (DME) in a sealed flask at 23 °C for 4 h. Trifluoromethanesulfonyl fluoride (bp −21 °C)[8] is generated in the reaction mixture and must be contained therein by the use of a tightly sealed reactor.[9,10] The one-flask procedure for the synthesis of vinyl triflates from the corresponding vinyl TBS-silyl ethers is general (see below) and likely involves CsF-induced enolate formation and trapping in situ by CF_3SO_2F.

Reaction of the bis-triflate **5** with 7 equiv of trimethylsilylmethylzinc bromide in THF (prepared in situ from equivalent amounts of TMS CH_2MgCl and $ZnBr_2$) at 23 °C in the presence of 5 mol % of $Pd(PPh_3)_4$ at 23 °C for 18 h provided the bis-allylic TMS derivative **6** in 92% yield. Tetracyclization of **6** to **1** was accomplished by exposure to 2.5 equiv of $MeAlCl_2$ in CH_2Cl_2 at

Scheme 1



−94 °C for 15 min, followed by treatment with tetra-*n*-butylammonium fluoride in THF at 23 °C for 1 h (to cleave any TMS ether of **1** which is present). Chromatography of the product on sg gave (+)-α-onocerin, mp 207−208 °C, $[\alpha]^{23}_D$ + 8.0 ($CHCl_3$) (31% overall yield from **2**), the structure of which was confirmed not only from its ^1H NMR, ^{13}C NMR, IR, and mass spectra[11] but also by X-ray crystallographic analysis. In addition to **1** (63% isolated yield of pure (+)-α-onocerin), a diastereomer was obtained in 9% yield which can be assigned the previously unknown structure **7** on the basis of spectroscopic analysis and the total synthesis which is summarized in Scheme 2. Unlike α-onocerin, which is a C_2-symmetric structure that shows only 15 peaks in the ^{13}C NMR spectrum and a two-fold simplification of the ^1H NMR spectrum, **7** exhibits 30 peaks in the ^{13}C NMR spectrum and many more proton peaks in the ^1H NMR spectrum than α-onocerin. For example, four separate proton resonances are observed for the terminal olefinic methylenes of **7**, further proof of a non-C_2-symmetric structure.

The synthesis of **7** sketched in Scheme 2 commences with the reaction of **2** with the dilithio derivative of 1,4-bisphenylsulfonylbutane (**8**) in THF at −78 °C to 20 °C to form stereoselectively

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Scheme 2

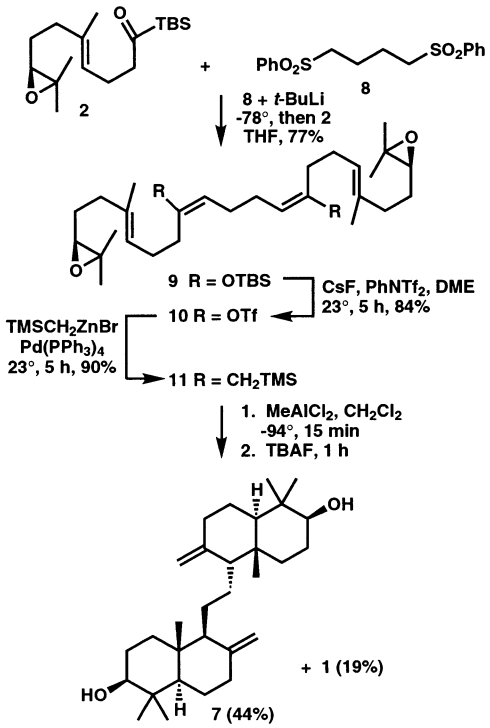
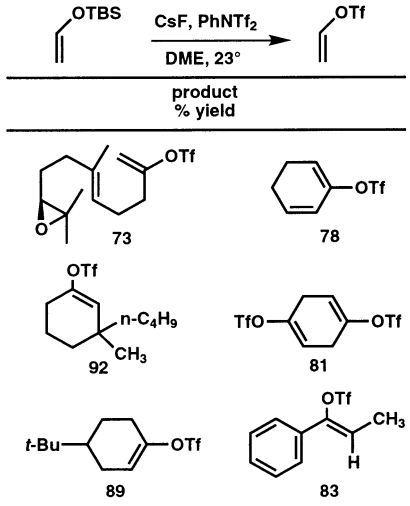


Table 1. Preparation of Vinyl Triflates from Vinyl TBS Ethers



the three-component coupling product **9** in 77% yield, the new olefinic linkages being formed only in the *E* geometry.[6b,e] The bis-vinyl-TBS-silyl ether **9** was converted, as above for **4** → **5**, into the corresponding bis-*E*-vinyl triflate **10**, and thence, as for **5** → **6** above, into the bis-allylic TMS compound **11**. Both **10** and **11** were isomerically pure (i.e., free of isomers **5** and **6**, respectively), as shown by 500 MHz ^{1}H NMR analysis. Tetracyclization of **11** using $MeAlCl_2$ in CH_2Cl_2 at −94 °C for 15 min (same conditions as for **6** → **1** + **7** in Scheme 1) gave, after fluoride treatment, the tetracycle **7** (44%) and, surprisingly, (+)-α-onocerin (19%). The transformations shown in Scheme 2 not only establish the structure and stereochemistry of **7** (when taken together with the spectral data) but also show conclusively that the $MeAlCl_2$-induced cation−olefin cyclizations of **6** and **11** (especially **11**) proceed to a significant extent through chair−boat A/B transition states (steroid A/B folding[7]). The chair−boat A/B pathway is clearly more favorable in the cyclization of the *E*,*E*-bis-allylic silane **11** than in the cyclization of the isomeric *Z*,*Z*-bis-allylic silane **6**.[12] We have previously reported an example of $MeAlCl_2$-induced tricyclization that proceeds exclusively via a chair−boat A/B closure route.[13] Our results show that the design of substrates that selectively favor one cyclization pathway over the other may be possible in chemical systems as well as for enzymes.[7,14]

As mentioned above, the stereocontrolled transformation of vinyl TBS ethers into the corresponding vinyl triflates (including *E* or *Z* geometry) proved useful in the above-described syntheses of **1** and **7** (Schemes 1 and 2). The process is quite general, as illustrated by the six examples in Table 1.[15]

The remarkably short and efficient (four steps, 31% overall yield) synthesis of **1** which has been presented in this paper demonstrates the power of modern synthetic chemistry and illustrates well the value of the underlying methodology.

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Supporting Information Available: Experimental procedures and physical data for the products shown in Schemes 1 and 2 (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Prolonged reaction time for the conversion of **4** to **5** should be avoided since **5** can undergo CsF-promoted elimination of CF_3SO_3 and the trans olefinic β-hydrogen to form an acetylenic linkage. The formation of **5** from **4** requires all the reactants, since it does not occur with CF_3SO_2F alone or with CF_3SO_2F−CsF mixtures in DME. It is apparent that the triflimide reagent plays a role in solubilizing CsF and promoting fluoride-induced silyl ether cleavage.
(10) The in situ generation of CF_3SO_2F results in a modest pressure (ca. 0.5 atm) buildup. Although CF_3SO_2F is commercially available, the in situ generation is both convenient and more economical. If CF_3SO_2F is allowed to escape from the reaction mixture, little or no vinyl triflate can be isolated.
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(12) (a) It is also noteworthy that the cyclization of **11** produces only two tetracyclic products, **7** (major) and **1** (minor), and no detectable (by 500 MHz ^{1}H NMR and TLC analysis) amount of the C_2-symmetric diastereomer of **1** that would result from a double chair−chair A/B folding cyclization pathway. (b) For a general review of cationic cyclization involving allylic silanes, see: Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063.
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(15) The following general procedure was used for the transformations of vinyl TBS ethers to vinyl triflates (eight examples) reported herein. Into a flame-dried, round-bottom flask flushed with dry N_2 and fitted with a magnetic stirrer were quickly placed dry $PhN(SO_2CF_3)_2$ (2−3 equiv), dry CsF (3−4 equiv, 1 equiv more than $PhN(SO_2CF_3)_2$, dried in vacuo for 12 h at 300 °C), and a solution of the vinyl TBS ether dissolved in DME (freshly distilled from sodium benzophenone ketyl). The flask was connected to a three-way stopcock by a ground glass joint sealed with Teflon tape to prevent the escape of gaseous CF_3SO_2F. Reactions were conducted with vigorous stirring under N_2 at 23 °C, followed by cooling of the contents, withdrawing a small sample by syringe, and analyzing by TLC or ^{1}H NMR. Upon completion of the reaction (or near completion in the case of triflates having *trans*-β-H to the triflate leaving group), the reaction mixture was vented and partitioned between pentane and pH 7 phosphate buffer. The aqueous phase was extracted with pentane or ether (for more water-soluble substrates), and the combined extracts were dried, concentrated in vacuo, and purified by rapid chromatography on silica gel.

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