First Synthesis of a Rearranged *neo*-Clerodane Diterpenoid. Development of Totally Regioselective Trisubstituted Furan Ring Assembly and Medium-Ring Alkylation Tactics for Efficient Access to (−)-Teubrevin G

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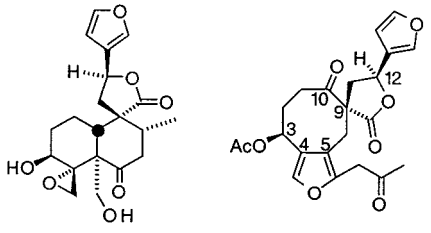
The clerodane and *neo*-clerodane diterpenoids occupy a uniquely important place in the natural product field because of the widespread distribution, extensive structural variation, and pronounced biological activity of these secondary metabolites.[1] While the vast majority of the members of this family is characterized by the presence of a decalin framework (e.g., teulepicin (**1**)),[2] a small group of offspring seco analogues have



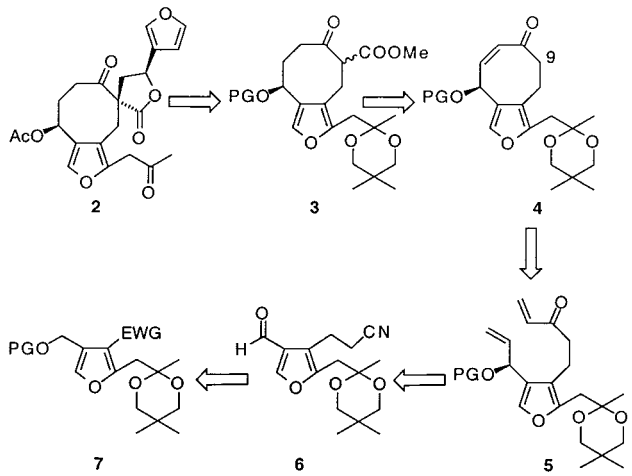
1 **2**

recently been isolated from the aerial parts of *Teucrium brevifolium*.[3] These structurally unique constituents exemplified by teubrevin G (**2**) feature a cyclooctanone core substituted in unusual fashion with fused and spirocyclic oxygen-containing rings, the ensemble of which causes **2** to be an intriguing synthetic target. The structural assignment to **2** was arrived at on the basis of spectroscopic data, including COSY, HMQC, NOESY, NOE, and HMBC NMR analysis. Here we report a direct enantioselective route to **2**. The central features of the approach are a fully regiocontrolled cycloaddition−retrograde fragmentation to form a 2,3,4-trisubstituted furan and the exploitation of a stereodefined alkylation in a medium ring context for the purpose of establishing the proper absolute configuration at C-9.[4]

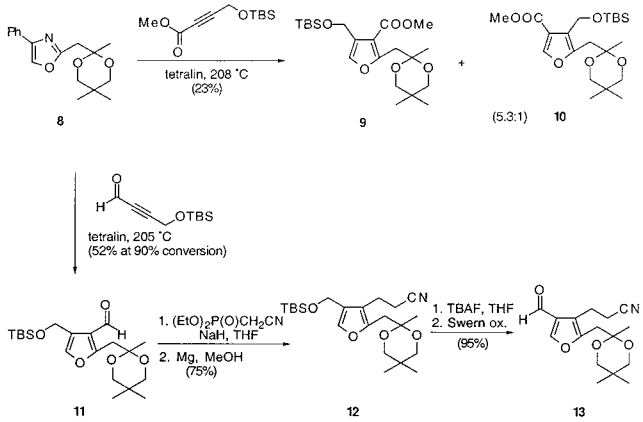
Retrosynthetically, we envisioned the alkylation of β-keto ester **3** to be a means potentially well suited to assembly of the γ-lactone (Scheme 1). Access to this advanced intermediate was to be gained by ring-closing metathesis of **5**, such that the C-acylation of **4** would materialize exclusively at C-9. The viability of this approach rested therefore on the availability of an expeditious means for generating the *monocyclic* 2,3,4-trisubstituted furans **6** and **7**, a family of heterocycles recognized not to be readily accessible.[5]

A key feature of the intramolecular [4 + 2] cycloaddition−retrofragmentation of alkyne-tethered oxazoles is the directed formation of *polycyclic* furans.[6] Intermolecular variants lack

Scheme 1



Scheme 2



comparable regioselectivity and have therefore been little utilized except with symmetrically substituted alkynes.[7,8] In light of this precedent, the conversion of **8**[9] in low yield to an inseparable 5.3:1 mixture of **9** and **10** was anticipated (Scheme 2). However, when we turned to the corresponding acetylenic aldehyde, **11** was produced as a single, easily purified regioisomer. A maximized yield of 52% was realized if the process was arrested at 90% conversion. It is noteworthy that the second possible furan was not detected under any circumstances, possibly indicative of previously unappreciated stereoelectronic factors.

Aldehyde **11** was subsequently transformed in an efficient two-step sequence[10] to **12**, from which **13** was obtained without event

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(4) The numbering is that originally proposed by Rodriguez et al.[3] and appears unusual because an attempt has been made to track the relocation of the carbon atoms during the ring-opening rearrangement.

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(8) This process appears to have been applied only once to construction of a 2,3,4- (Yadav, J. S.; Valluri, M.; Rao, A. V. R. *Tetrahedron Lett*. **1994**, *35*, 3609) and a 2,3,5-trisubstituted furan (Iesce, M. R.; Cermola, F.; Graziano, M. L.; Scarpati, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 147).

(9) Oxazole **8** was prepared by sequential reaction of the known acetal of methyl acetoacetate (Zamir, L. O.; Sauriol, F.; Nguen, C.-D. *Tetrahedron Lett*. **1987**, *28*, 3059. Chan, T. H.; Brook, M. A.; Chaly, T. *Synthesis* **1983**, 203) with ammonium hydroxide and then with phenacyl bromide in toluene at 100 °C.

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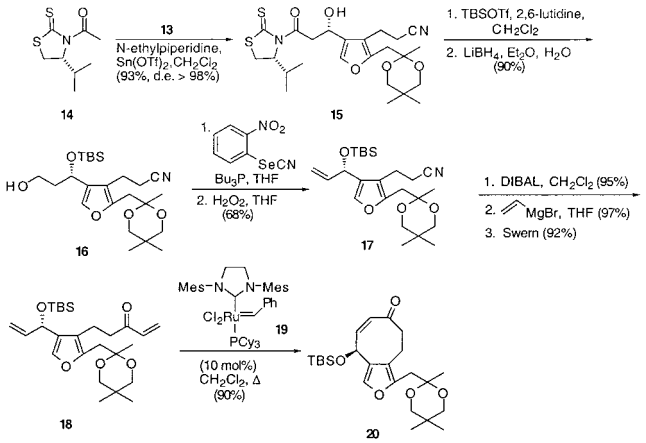
Scheme 3

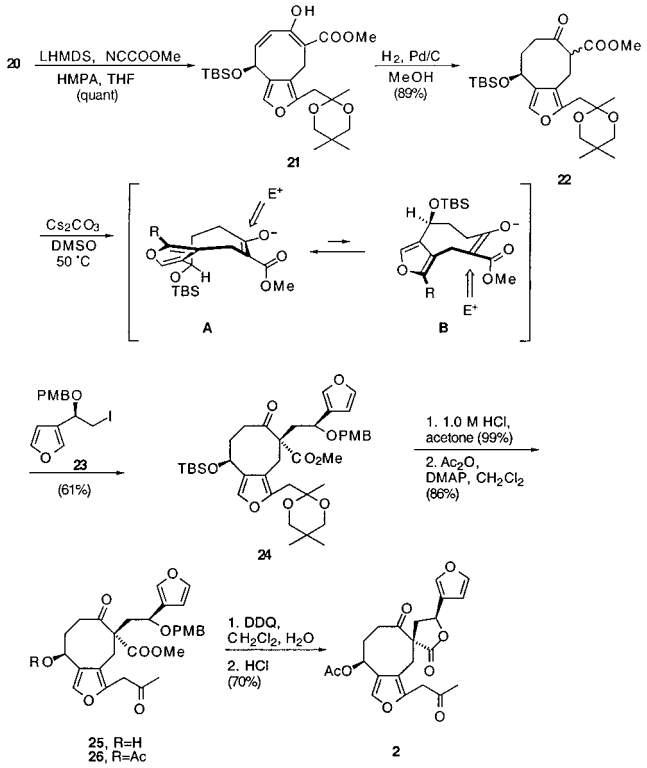


by desilylative oxidation. The availability of this aldehyde permitted proper enantiocontrolled introduction of the C-3 hydroxyl group by application of Nagao's chiral 1,3-thiazolidine-2-thione technology[11] (Scheme 3). The *N*-acetyl derivative **14** enters smoothly into aldol condensation with **13** to furnish **15** in 80% yield at a de level of 98%. The β-hydroxy amide was next silylated and subjected to lithium borohydride reduction.[12] Chemoselective Grieco dehydration[13] of the resulting primary carbinol **16** followed by Dibal-H reduction, treatment with vinylmagnesium bromide, and Swern oxidation gave rise to dienone **18**, whose role it was to serve as the precursor to a 3,4-cyclooctenofuran.

When recourse was made to Grubbs' catalyst[14] for the ring-closing metathesis step, only very modest yields of **20** (20−35%) were realized, and only after use was made of long reaction times (>3 days) and high catalyst loadings (30−35 mol %). Use of copper(I) salts[15] increased the level of conversion to ~50%, but the requisite proportion of catalyst remained high. A very practical resolution to this problem was uncovered in the form of **19**.[16] This ruthenium complex delivered **20** in 90% yield when employed at the 10 mol % level in refluxing CH_2Cl_2 for 34 h.

With the eight-membered ring in place, we began installation of the remaining eastern sector of **2**. As anticipated,[17] the deprotonation of **20** with lithium hexamethyldisilazide was directed away from the OTBS substituent, thereby allowing for efficient conversion to the enolized β-keto ester **21** with Mander's reagent[18] (Scheme 4). The superfluous double bond in **21** was saturated cleanly without reducing the furan ring by conventional hydrogenation over Pd/C. Considerable experimentation was required to uncover reaction conditions that would cause the enolate anion of **22** to be alkylated by iodide **23**.[19] The use of cesium carbonate in warm DMSO uniquely afforded useful yields

Scheme 4



of **24** (61%) and its easily separated diastereomer (15%). The stereochemical course of this bond-forming protocol can be rationalized in terms of the preferred adoption of conformer **A** in the low-energy transition state as a consequence of the quasi-equatorial projection of the distal OTBS substituent. In spatial arrangement **A**, an unfavorable gauche interaction with the furan ring is also operational. However, the significantly less sterically encumbered top surface of **A** is particularly conducive to optimal kinetic control.

Treatment of **24** with mineral acid in acetone induced the selective hydrolysis of two protecting groups. The free hydroxyl substituent in **25**, although unusually sluggish toward acetylation, was efficiently transformed into **26** when promoted by DMAP. Arrival at (−)-teubrevin G (**2**) was ultimately achieved via oxidative removal of the PMB group with DDQ and lactonization under aqueous acidic conditions. The assembly required 21 steps from **8** and proceeded in 5.2% overall yield. The synthetic product was identical in all respects with the literature spectral data (^{1}H and ^{13}C NMR, IR, HRMS) and chiroptical properties.[20]

In conclusion, a synthesis of (−)-teubrevin G has been achieved by a series of regiocontrolled tactics including a one-step route to a 2,3,4-trisubstituted furan, generation of a highly substituted 2-cyclooctenone by ring-closing metathesis, and reliance on remote asymmetric induction to establish the absolute configuration of the spirocyclic carbon.

Supporting Information Available: Representative experimental procedures and spectroscopic data (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

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(19) This reagent was prepared from 3-vinylfuran via asymmetric dihydroxylation by analogy to the 2-isomer (Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982). The (2*R*)-diol of >90% ee was condensed with *p*-methoxybenzaldehyde dimethylacetal, reduced with Dibal-H, and exposed to triphenylphosphine diiodide.

(20) An $[\alpha]_D^{22}$ of −69.6 (*c* 0.46, $CHCl_3$) was measured for (−)-**2**. The reported rotation of the natural substance is $[\alpha]_D^{21}$ −64.1 (*c* 0.382, $CHCl_3$).[3]