ORGANIC LETTERS

2010
Vol. 12, No. 15
3418−3421

# Synthesis of the Guaianolide Ring System via Cycloaddition of a Bicyclic Carbonyl Ylide with Allyl Propiolate

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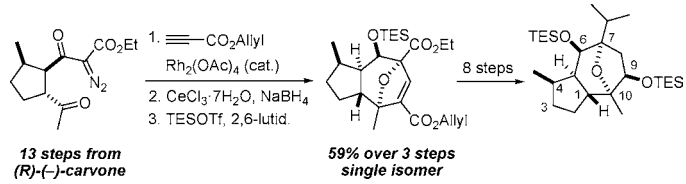
**Received May 26, 2010**

## ABSTRACT




**A cyclic carbonyl ylide with a *trans*-annulated cyclopentane ring was generated by a $Rh_2(OAc)_4$-catalyzed reaction from a diazoketone precursor and trapped with allyl propiolate. The 1,3-dipolar cycloaddition led to the stereoselective formation of an oxygen-bridged polycycle. Via Curtius degradation, the cycloadduct was transformed to the ring skeleton typical of the sesquiterpene family of guaianolides.**

Terpenes represent one of the largest groups of natural products. These secondary metabolites can be divided into subgroups based on the number of isoprenoid units.[1] A large subgroup is sesquiterpenes which originate from farnesyl diphosphate.[2] Among various ring systems that result from this precursor, the perhydroazulene skeleton, which is characterized by fused five- and seven-membered rings, is quite common. The core structures might differ in the oxidation level and the relative stereochemistry at the ring fusion. Some of these guaiane-type terpenes feature an oxygen bridge in the seven-membered ring (Figure 1).[3]

A recent addition to oxygen-bridged guaianes are the englerins (**6**−**8**), sesquiterpenes that were isolated from the plant extract of *Phyllanthus engleri* (Figure 2).[4] Besides the structural features, the biological activity, for example

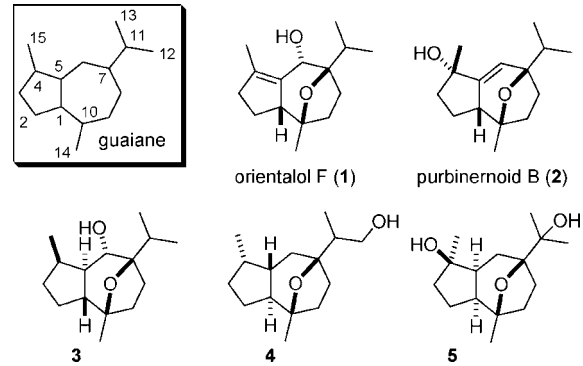



**Figure 1.** Examples for oxo-bridged guaiane-type natural products.

of englerin A (**6**), is remarkable in that it turned out to be highly selective and potent against various cell lines that are involved in renal cancer. Accordingly, englerin A (**6**) became a prominent target for total synthesis. In the original

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**Published on Web 06/29/2010**

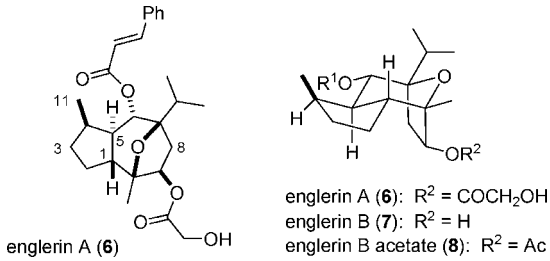
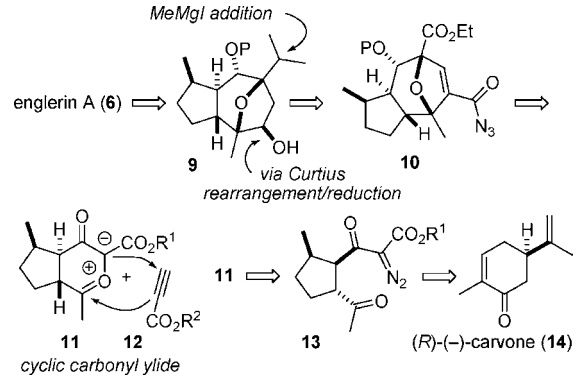



**Figure 2.** Correct structure of (−)-englerin A (**6**).

publication,[4] the absolute stereochemistry was not known, and the enantiomer of **6** was depicted. This issue could be clarified in nice work by the group of M. Christmann.[5] They prepared *ent*-**6** [(+)-englerin A] from *cis*,*trans*-nepetalactone, a terpene which can be obtained by distillation of commercially available catnip. Quite recently, two conceptually similar total syntheses for (−)-englerin A appeared.[6,7] In both cases, the tricyclic ring system was fashioned by gold(I)-catalyzed cyclization of an enyneketone.[8] In addition, the Nicolaou/Chen group achieved the synthesis of englerin A via a [5 + 2] cycloaddition to create the [3.2.1]oxabicyclic ring system followed by annulation of the cyclopentane ring.[9]

In planning a synthesis for oxygen-bridged guaianolides,[10] like englerin A, the stereochemistry at the fusion bond needs to be considered. This issue might be addressed by epimerization en route to the target skeleton.[11] Besides five- or seven-membered rings, natural products, like (+)-aromadendrene[12] or other easily available precursors[13] with a guaianolide structure, might serve as starting materials. The key feature of our retrosynthesis is a bimolecular carbonyl ylide−alkyne cycloaddition reaction (Scheme 1).[14,15] The advantage of this strategy is the simultaneous formation of

**Scheme 1.** Retrosynthetic Plan for Construction of Oxygen-Bridged Guaianolides Based on a Carbonyl Ylide−Alkyne 1,3-Dipolar Cycloaddition




the oxygen bridge in the course of the cycloaddition. Thus, after appropriate functional group interconversions, carbonyl ylide **11** would be combined with a propiolate **12**. The intermediate carbonyl ylide should be available by rhodium(II)-catalyzed decomposition of diazoketoester **13**. The latter can be traced back to (*R*)-(−)-carvone (**14**). The hydroxyl group at C9 would be generated from the carboxylic acid azide. The expectation was that the dipolarophile would approach the carbonyl ylide **11** opposite to the C4 methyl group.

The results of this strategy are described below (Scheme 2). Starting from commercially available (*R*)-(−)-carvone (**14**), the highly substituted cyclopentane **16** (Scheme 2) was prepared utilizing a five- step sequence that relies on epoxidation of the enone, regioselective epoxide opening, and a Favorskii rearrangement resulting in ring contraction to a cyclopentanecarboxylate.[16,17] Removal of the THP protecting group gave alcohol **16** on a multigram scale. The hydroxyl

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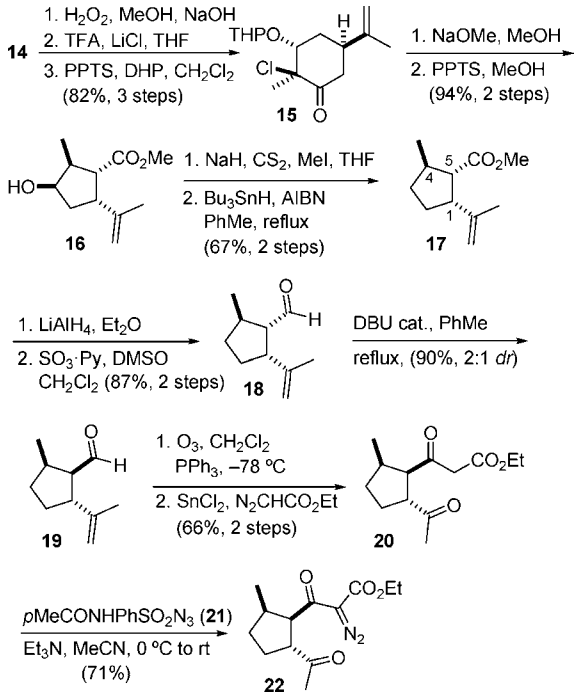
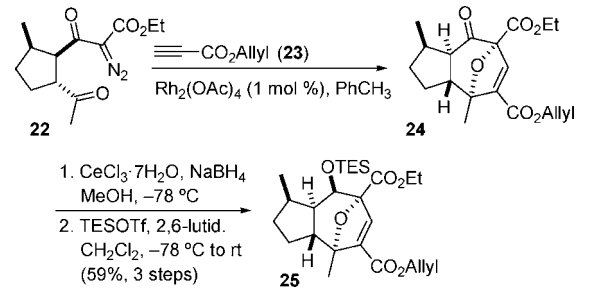
**Scheme 2.** Synthesis of Diazoketone **22** from (*R*)-(−)-Carvone




group was then removed yielding ester **17** using the Barton−McCombie protocol[18] on the corresponding xanthogenate. At this stage, we tried epimerization at C5 (guaiane numbering); however, this was not successful with several bases (DBU, *i*Pr$_2$EtN, LDA, Et$_3$N). Therefore, the ester was reduced to the alcohol which was then converted to aldehyde **18** by Parikh−Doering oxidation[19] on a 25 g scale (87%). Base-induced epimerization of aldehyde **18** was achieved with DBU in refluxing toluene leading to *trans* orientation of the aldehyde group with respect to the larger isopropenyl group (*trans*/*cis* = 2:1). Subsequent ozonolysis of aldehyde **19** and reaction with ethyl diazoacetate, catalyzed by tin(II) chloride,[20] provided $\beta$-ketoester **20** as a single isomer in 66% over two steps (the other diastereomer was not detected). Finally, a diazotransfer reaction with sulfonyl azide[21] **21** furnished diazoketone **22**. This sequence allowed us to prepare gram quantities of diazo $\beta$-ketoester **22** starting from (*R*)-(−)-carvone.

With diazoketone **22** in hand, we studied the intramolecular carbonyl ylide formation promoted by Rh$_2$(OAc)$_4$ and its subsequent cycloaddition (Scheme 3). We decided to use allyl propiolate (**23**) as a dipolarophile due to ease of further functionalization. After careful experimentation, we found that heating of a mixture containing allylester **23**, 1 mol % of Rh$_2$(OAc)$_4$, and diazo compound **22** in toluene (100 °C)

**Scheme 3.** Rh$_2$(OAc)$_4$-Catalyzed Carbonyl Ylide Formation and Subsequent 1,3-Dipolar Cycloaddition with Allyl Propiolate




for 15 min led to the formation of cycloaddition product **24** as a single isomer. Lower temperatures and longer reaction times gave inferior results [80 °C, 1 h (80%); 60 °C, 12 h (50%)]. The cycloadduct **24** turned out to be sensitive to epimerization, for example, upon silica gel chromatography, leading exclusively to the corresponding *cis*-isomer. Therefore, crude ketodiester **24** was selectively reduced with $NaBH_4$ and the resulting alcohol converted to TES-ether **25** in 59% over three steps. At this stage we were not able to unambiguously determine the stereochemistry of the newly formed centers. This could be clarified at a later stage (vide infra).

Further functionalization of the seven-membered ring called for degradation of the acrylate to a keto function. This could be achieved via a classical Curtius rearrangement/hydrolysis sequence (Scheme 4).[22] It was found that the allyl ester could be easily cleaved using 10 mol % of RhCl(PPh$_3$)$_3$ in an ethanol/water mixture at 100 °C in 84% yield.[23] In contrast, palladium-based methods failed to provide carboxylic acid **26**. Now, acid **26** was converted to azide **27** by reaction with $NaN_3$ in the presence of trichloroacetonitrile and $PPh_3$.[24] Upon heating, azide **27** rearranged to the vinyl isocyanate which under acidic conditions was selectively hydrolyzed to ketone **28**. It should be noted that under these conditions [HCl (5%), THF, rt] no deprotection of the TES group was observed. Subsequent reduction with $NaBH_4$ provided alcohol **29** as a single isomer. At this stage, key NOESY cross peaks between 1-H/8-H, 4-H/5-H, and 5-H/6-H (guaianolide numbering) suggested a structure of **29** where the oxygen bridge is on the opposite site with respect to the C4 methyl group (Scheme 4). Nevertheless, we continued with further functional group manipulations that would allow for either a chemical correlation with a known compound or an X-ray structure. Silyl protection to bis-silyl ether **30** served as an entry point for further synthetic modifications which aimed at conversion of the ester to an isopropyl group. Accordingly, addition of freshly prepared MeMgI (6 equiv) to ester **30** at 0 °C gave tertiary alcohol **31** in quantitative yield. While a radical deoxygenation did

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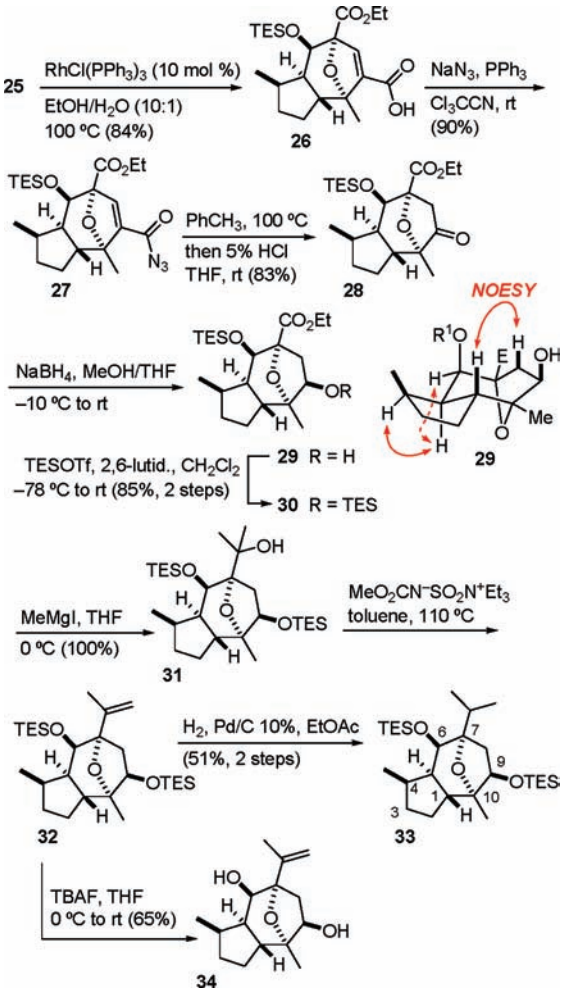
**Scheme 4.** Transformation of Cycloadduct **25** into Oxa-Bridged Guaianolides **33** and **34**




not work, neither on the corresponding xanthogenate nor trifluoro acetate, alcohol **31** could be easily dehydrated with Burgess reagent[25] ($MeO_2CN^-SO_2N^+Et_3$) to give alkene **32** which led to guaianolide **33** via catalytic hydrogenation. TES deprotection on alkene **32** could be achieved with TBAF to give alkenediol **34** in reasonable yield.

Crystallization of **34** from a hexane/diethyl ether mixture provided crystals suitable for X-ray analysis (Figure 3) indicating the configuration of the stereocenters and conformation of the structure. The C3 methylene group could not be exactly localized. The X-ray structure additionally proved the facial selectivity in the cycloaddition step which corroborated the NOESY data of compound **29**. It is difficult to rationalize the facial selectivity of the cycloaddition reaction with the dipolarophile approaching *syn* to the

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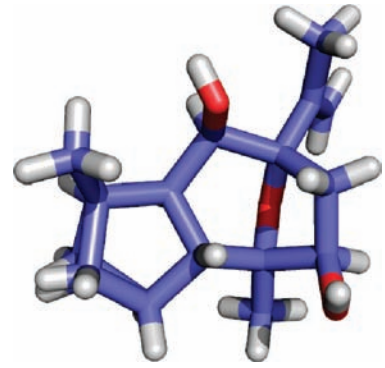

**Figure 3.** Rendering of the X-ray structure of tricyclic compound **34**.

cyclopentane methyl group. Calculations (Spartan 08) showed a half chair conformation of the six-membered carbonyl ylide (see Supporting Information). One explanation for the diastereoselectivity might be pyramidalization of the reacting centers in the dipole.[26,27]

In summary, we demonstrated that oxo-bridged guaiane-type structures can be accessed via a rhodium(II)-catalyzed carbonyl ylide formation/cycloaddition strategy. In the case at hand, (*R*)-(−)-carvone served as a chiral starting material which allowed us to prepare diazo *β*-ketoester **22**. A high facial selectivity was observed in the cycloaddition step. On the tricyclic cycloadduct **24**, the seven-membered ring was functionalized via Curtius rearrangement/hydrolysis sequence of an unsaturated carbonyl azide. Further studies on the facial selectivity of related cycloadditions and application of the present strategy toward the total synthesis of oxa-bridge sesquiterpenes (Figure 1) is in progress in our laboratory.

**Acknowledgment.** Financial support by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. In addition, a 10 month DAAD fellowship for D. B. Ushakov (Universität Tübingen) is acknowledged as well. This work was carried out within the framework of COST action CM0804 - Chemical Biology with Natural Products.

**Supporting Information Available:** Experimental procedures and characterization for all new compounds reported and copies of NMR spectra for important intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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