Synthesis (in *ent*-form) of a Novel Jalcaguaianolide from *Ferula arrigonii* Bocchieri

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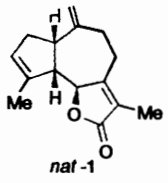
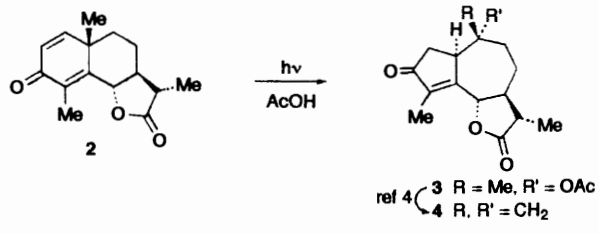
A recently isolated isodehydrocostus lactone from the genus *Ferula* (Umbelliferae) has been stereoselectively prepared in *ent*-form from α-santonin by photochemical transformation to *O*-acetylisophotosantonic lactone followed by functional group manipulations that conclude with a one-step γ-butyrolactone → $\Delta^{\alpha,\beta}$-butenolide conversion; the synthesis corroborates both the structure and the relative and absolute stereochemistry that have been proposed for the natural product.

α-Santonin is an often-used starting material for terpenoid synthesis because of its ready availability and rich functionality.[1] α-Methylene-γ-butyrolactones figure significantly among the natural products that have been prepared to date from this γ-butyrolactone, but the $\Delta^{\alpha,\beta}$-butenolides have, surprisingly, yet to be effectively addressed.[2] Here we report the first preparation of the novel isodehydrocostus lactone **1**, a jalcaguaianolide derivative recently isolated from *Ferula arrigonii* Bocchieri (Umbelliferae) and elucidated spectroscopically.[3a] This direct synthesis, which we believe also to be the first of any natural guaiane $\Delta^{\alpha,\beta}$-butenolide (but in the *ent*-series), serves to establish the structure and the relative and absolute stereochemistry of the natural product.



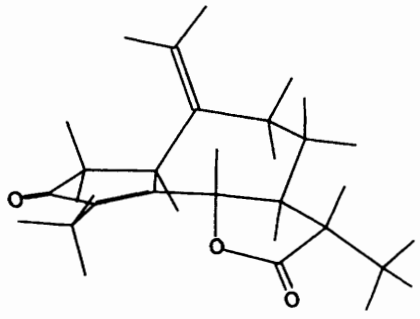
nat-1

Our starting material, the dienone lactone **4**, was available in 63% yield from *O*-acetylisophotosantonic lactone **3**,[4] a photoproduct from α-santonin **2**.[5]



The α-face-selective hydride conjugate addition earlier observed[6] on treatment of **4** with sodium borohydride in pyridine (Scheme 1) reflects the relative encumbrance that is present on the β-face of the dienone, which can be readily appreciated by inspection of the depicted global minimum energy conformation † of the molecule. Steric approach control is also seen in the selective reduction[4] of the derived toluene-*p*-sulfonylhydrazone (**4**→**7**). In that dehydration of **5** to afford **6**, the planned precursor of **1**, had in earlier work been found to be very low yielding,[6] we sought to secure this diene by exploiting the preference for α-face approach to generate

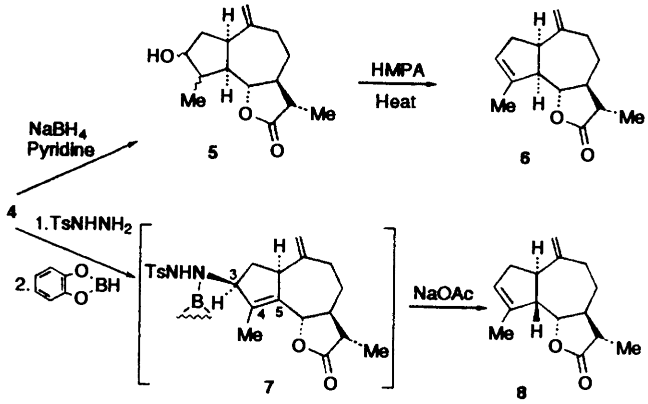
† Insight II Discover, version 2.1.2 (Biosym Technologies). The depicted conformation is lowest in energy by 1.9 kcal mol^{-1}.



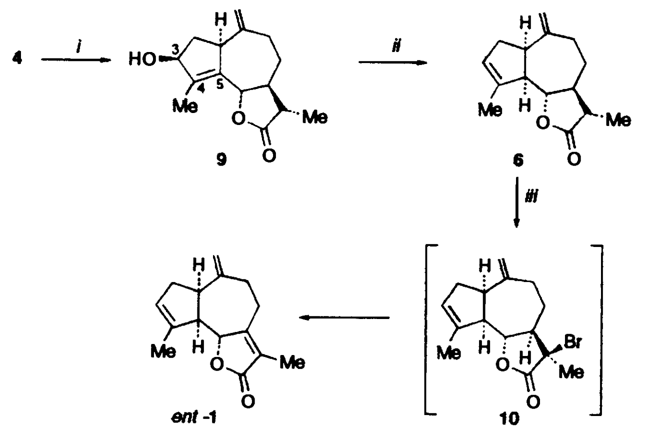
selectively the C-3 toluene-*p*-sulfonhydrazide α-epimer, which on decomposition would be expected to furnish **6**.[4]

The dienone **4** on reduction with sodium borohydride in ethanol (Scheme 2) gave in 74% yield the β-alcohol **9** (containing *ca.* 15% of the α), which in nitromethane in the presence of an excess of toluene-*p*-sulfonhydrazide underwent conversion into the hydrazide derivative.[7] Without isolation this material, presumably a mixture comprised mostly of the α-epimer, was treated with sodium acetate in acetic acid to effect transformation to the diazene, which through [3,3] sigmatropic rearrangement delivered a hydrogen at C-5 with $\Delta^4 \rightarrow \Delta^3$ double-bond transposition to provide the desired diene **6**, together with the 5β epimer, as a separable 2:1 mixture in 55% overall yield. While this preparation of **6** is not yet as efficient as we would like, it nevertheless represents a significant improvement over the previously used approach to this compound.

The lactone **6** on phenylselenenylation–oxidative *syn* elimination had earlier been found to yield exclusively the corresponding α-methylene-γ-butyrolactone derivative.[6] This taken together with related results[8] suggested that bromination of the lactone enolate of **6** should selectively provide the β-bromide **10**, and that this compound on base treatment might undergo mainly endocyclic *anti* elimination to yield the desired butenolide. To our delight, reality improved on this scenario: the derived bromide, presumed to be **10** but at no point detectable, suffered spontaneous elimination under the reaction conditions and gave in *ca.* 70% yield *exclusively* the jalcaguaianolide derivative **1**. The synthetic product provided high field proton and carbon-13 NMR, IR, and mass spectra in complete agreement with those of an authentic sample of the natural metabolite, however its specific rotation, although equal in magnitude, was opposite in sign.* *Thus*, nat-**1** *correctly depicts the structure and the relative and absolute stereochemistry of the natural product.*



Scheme 1



Scheme 2 *Reagents and conditions:* i, $CeCl_3$, EtOH, −15 °C, then $NaBH_4$, 1.5 h; ii, $TsNHNH_2$, $MeNO_2$, 4 ° C, 72 h, then AcOH, AcONa, 50 °C, 2 h; iii, LDA, −78 to −50 °C, 1 h, then −78 °C, $BrCH_2CH_2Br$, HMPA, −78 to 0 °C, 3 h.

Experimental

Jalcaguaianolide ent-**1** *from the Dienone* **4**.—To a stirred solution of the dienone **4**[4] (1.30 g, 5.28 mmol) in absolute ethanol (19 cm^3) was added cerium(III) chloride heptahydrate (2.07 g, 5.56 mmol). After dissolution was complete, the solution was cooled to −15 °C and treated portionwise over 15 min with sodium borohydride (231 mg, 6.10 mmol). After being stirred at this temperature for 1.5 h, the reaction mixture was processed with ether in the usual way and the crude product was purified by dry-column chromatography on silica gel with 35% ethyl acetate in hexane to give **9** (971 mg, 74%, containing *ca.* 15% of the α-isomer).

A sample of this material (90 mg, 0.36 mmol) was stirred with toluene-*p*-sulfonhydrazide (725 mg, 0.36 mmol) in nitromethane (12 cm^3) at 4 °C for 72 h, whereupon a solution of 5% sodium acetate in acetic acid (1.5 cm^3) was added and the resulting solution was heated at 50 °C for 2 h. The crude product was isolated with ether in the usual way and filtered over 70–230 mesh silica gel with 10% ethyl acetate in hexane to provide a 2:1 mixture (46 mg, 55%) of the *cis* and *trans* trisubstituted olefins **6** and **8**, respectively, which were separated by careful chromatography on 230–400 mesh silica gel with 10% ethyl acetate in hexane and identified through comparison with independently prepared samples.[4,6]

To a 0.19 mol dm^{-3} solution of lithium diisopropylamide in THF (1.8 cm^3, 0.34 mmol) at −78 °C was added with stirring the diene **6** (31 mg, 0.13 mmol) in THF (0.80 cm^3). The resulting solution was allowed to warm to −50 °C over 1 h, after which it was again cooled to −78 °C and treated with 1,2-dibromoethane (0.415 cm^3; 905 mg, 4.82 mmol) in HMPA (0.415 cm^3). The reaction mixture was allowed to warm to 0 °C over 3 h and then treated with aqueous ammonium chloride. The crude product was isolated with ether in the normal way and purified by dry-column chromatography on silica gel with 5% ethyl acetate in hexane to give recovered **6** (7 mg) followed by **1** (19 mg, 62%; 80% based on consumed **6**) as an amorphous solid. The NMR, IR, and mass spectral data of this material were in complete agreement with the reported[3a] values and with those obtained from an authentic sample of the natural product. Furthermore, the synthetic and natural compounds showed identical TLC behaviour on multiple elution with several different solvent systems: $[\alpha]_D^{20}$ +152 (*c* 0.4 in $CHCl_3$) (see footnote) [Found: M^+ (EI), 230.1306. $C_{15}H_{18}O_2$ requires *M*, 230.1307].

* The reported[3a] specific rotation of the natural product, while also opposite in sign to that of the synthetic material, was distinctly lower in magnitude. However, the authentic material that we ourselves isolated from the same plant (and whose identity with the originally isolated, but no longer available, sample was unequivocally established by direct spectral comparison) provided $[\alpha]_D$ −155 *vs.* +152 for the synthetic substance.

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