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TOTAL SYNTHESIS OF THE GERMACRANOLIDE (±)-ARISTOLACTONE VIA [2,3] WITTIG RING CONTRACTION

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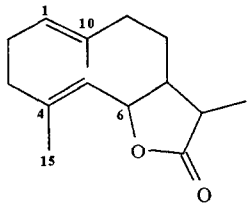
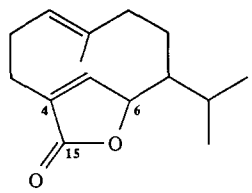
Summary: The total synthesis of (±)-aristolactone (**15**) is described wherein the key cyclodecenynol precursor **10** is prepared in over 90% yield via a highly regio and stereoselective [2,3] Wittig rearrangement of the 13-membered propargylic ether **9**.

The germacranolides comprise the largest subgroup of sesquiterpene lactones with some 300 known variants.[1] Many possess a bridged lactone moiety linking C-15 with a C-6 oxygen substituent.[1,2] A number of these exhibit unusual properties as a result of the close transannular proximity of double bonds and the bridging lactone ring. In several instances distinct conformers can be seen in the ^{1}H NMR spectrum at room temperature.[2a,b]

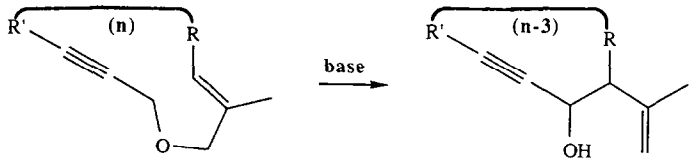


germacranolide



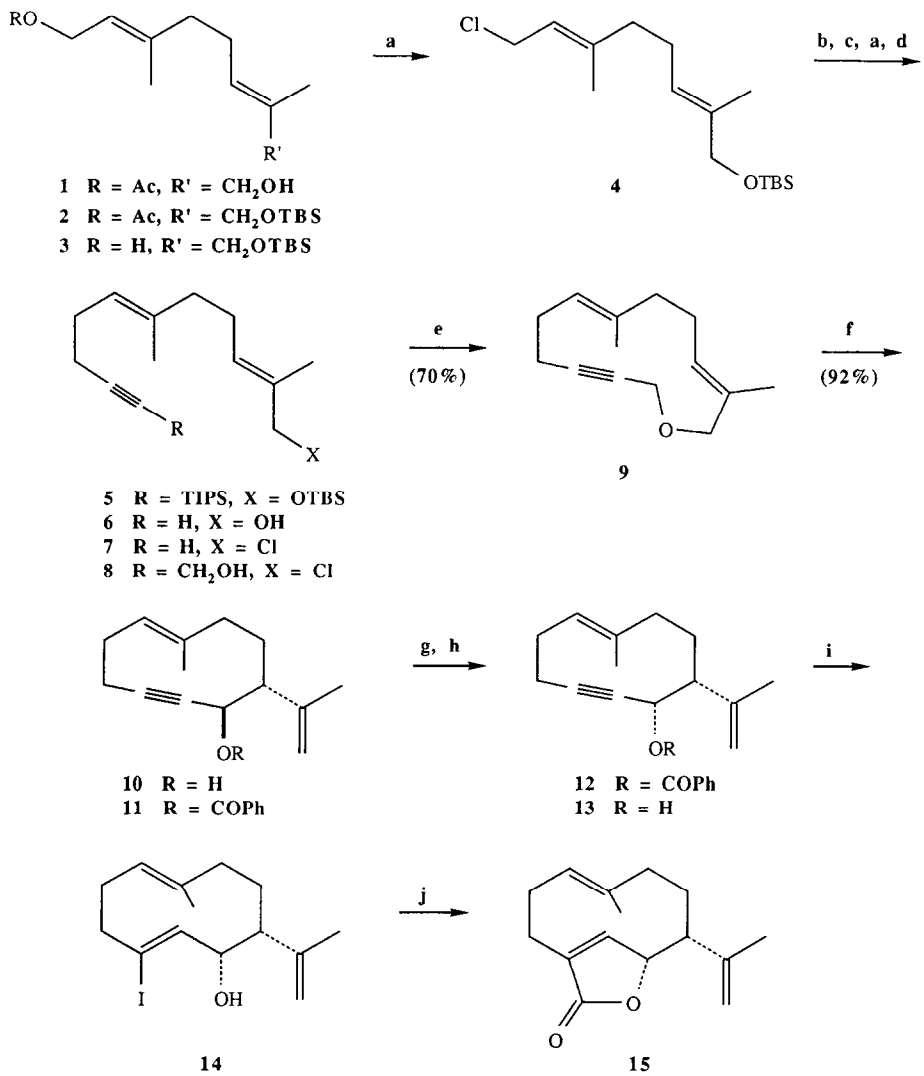
bridged germacranolide

We recently disclosed a novel route to cembranoids via [2,3] Wittig ring contraction of macrocyclic allylic propargylic ethers (I → II, n = 17).[3] We now describe a remarkably efficient application of that strategy to the synthesis of cyclodecenyne precursors of bridged germacranolides from 13-membered ethers (I → II, n = 13).[4]



I II

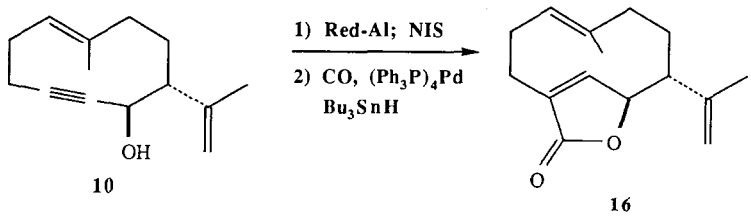
Our route commences with the allylic alcohol **3** prepared via SeO_2 oxidation of geranyl acetate[5] followed by silylation (TBSCl, Et_3N, DMAP) and saponification (K_2CO_3, MeOH). The chloride **4**[6] underwent smooth α,α-coupling with TIPS protected[7] propargylmagnesium bromide-CuI to give the dienyne **5**. Silyl cleavage with (n-Bu)$_4$NF gave the alcohol **6** which was directly converted to the chloride **7** via the Collington-Meyers procedure.[6] Addition of paraformaldehyde to the derived lithio acetylide afforded the chloro alcohol **8**. Cyclization of **8** was effected by treatment with 1 equiv. of EtMgBr in THF-HMPA, initially at 0°C, with gradual warming to reflux, all at moderate (0.02 *M*) dilution. The 13-membered ether **9** was thereby obtained in 70% yield. This ether underwent a remarkably facile rearrangement upon stirring with n-BuLi in pentane-THF at -78°C for 2.5 h to afford the propargylic alcohol **10**, a single isomer by high field ^{1}H and ^{13}C NMR analysis, in over 90% yield. From mechanistic considerations[8,3] we expected alcohol **10** to possess the trans stereochemistry. This point was confirmed as follows:



a) MsCl, LiCl, DMF, 2,6-lutidine; b) TIPSC≡CCH_2MgBr, CuI, THF, -20°C; c) $(n\text{-Bu})_4NF$, THF; d) *n*-BuLi, $(CH_2O)_n$, THF, -78°C to 23°C; e) EtMgBr, THF, HMPA, 0°C to reflux, 0.02 *M*, 4 h; f) *n*-BuLi, pentane-THF (9:1), -78°C, 2.5 h; g) EtOCON=NCO_2Et, Bu_3P, THF, $PhCO_2H$; h) K_2CO_3, MeOH; i) Red-Al, THF, 23°C; NIS, -78° to 0°C; j) $(Ph_3P)_4Pd$, Bu_3SnH, CO, toluene, 53°C, 2.5 h.

Treatment of **10** with DEAD, Ph_3P and $PhCO_2H$ afforded the benzoate **12**.[9] Such reactions are well known to proceed with inversion of configuration. Indeed, benzoate **12** was clearly different (^1H NMR) from the crystalline derivative **11** (mp 80-81°C) prepared from **10** with PhCOCl in pyridine. Saponification of the inverted benzoate **12** yielded the presumed cis alcohol **13**, distinctly different (^1H and ^{13}C NMR) from the [2,3] Wittig product **10**. Alcohol **13**, upon treatment with Red-Al followed by N-iodosuccinimide[11] was converted to the unstable iodide **14**. This highly sensitive iodo alcohol was immediately treated, without purification, with CO in the presence of $(Ph_3P)_4Pd$ and Bu_3SnH in toluene[12] to afford the crystalline lactone **15**, (±)-aristolactone,[2c] mp 87-88°C, whose identity was ascertained through comparison with natural aristolactone.[13]

As an added check the [2,3] Wittig product, alcohol **10**, was subjected to the foregoing reduction-iodination, carbonylation sequence whereupon the bridged lactone **16**, mp 61-62°C, was obtained. The spectral products of this lactone clearly differed from those of aristolactone.



10 **16**

Though sharply melting and pure by TLC analysis, **16** exhibited two sets of vinylic proton and methyl peaks in the ^1H NMR spectrum in the ratio 70:30 suggestive of slowly interconverting conformers. Such behavior has been previously noted with related bridged lactones.[2a,b] Interestingly, the ^1H NMR spectrum of aristolactone shows only a single set of peaks at room temperature, consistent with rapidly interconverting conformers. Models indicate that with the isopropenyl grouping in an "equatorial" orientation the cyclodecadiene ring adopts a much more open conformation for the cis isomer **15** than for the trans isomer **16** thereby allowing a more facile "jump rope" rotation of the trisubstituted double bond in the former.

The [2,3] Wittig ring contraction thus provides an efficient route to cyclodecenyne precursors of germacranolide bridged lactones. The reaction is completely regio and stereoselective to the limits of detection by high field ^1H NMR. Moreover, both critical steps, cyclic ether formation and the rearrangement itself proceed in excellent yield.

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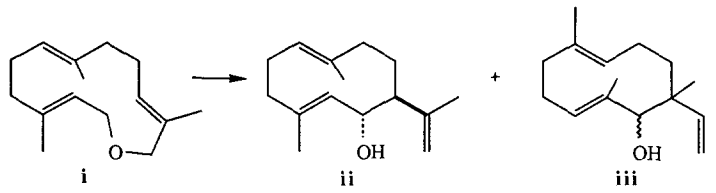
4. A related route involving [2,3] Wittig rearrangement of 13-membered diallylic ethers has recently been reported. The rearrangement proceeds in high yield with excellent stereoselectivity, but a 75:25 mixture of regioisomers is produced (i → ii + iii).



i ii iii

75 : 25

Takehashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315. We thank Professor Takehashi for informing us of his results prior to publication.

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13. A sample of natural aristolactone and copies of spectra were kindly provided by Professor G. L. Lange, Guelph, Ontario.

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