The first total synthesis of (±)-pallescensin B

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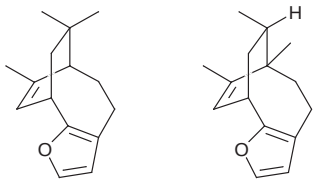
Received (in Cambridge, UK) 9th November 1998, Accepted 20th November 1998

The first total synthesis of the title compound has been accomplished using an intramolecular Diels–Alder reaction of a masked *o*-benzoquinone, anionic [1,3]-rearrangement of a vinylbicyclo[2.2.2]octenol and intramolecular hetero-Michael addition of a hydroxy enone as the key steps.

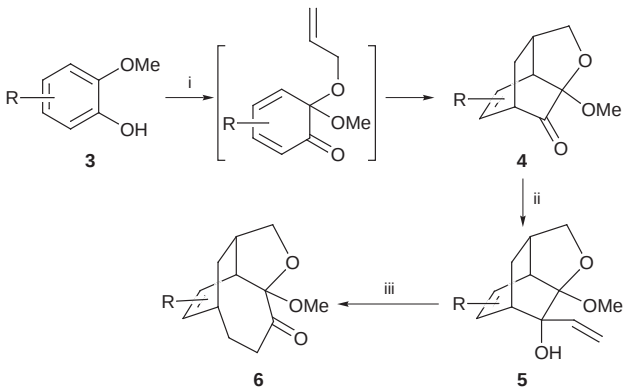
Pallescensins are a group of furanosesquiterpenoids isolated from the marine sponge *Disidea pallescens* by Cimino *et al*.[1] The common feature of these terpenoids is that they all contain a furan moiety; however they have carbon skeletons of varying complexity. Among the pallescensins, pallescensin B **1** presents the most complex architecture, with a unique bicyclo[4.2.2]decane system fused to a furan moiety. Interestingly, bicyclo[4.2.2]decane skeletons are relatively rare among natural products, the only other known example being nakafuran-8 **2**.[2]



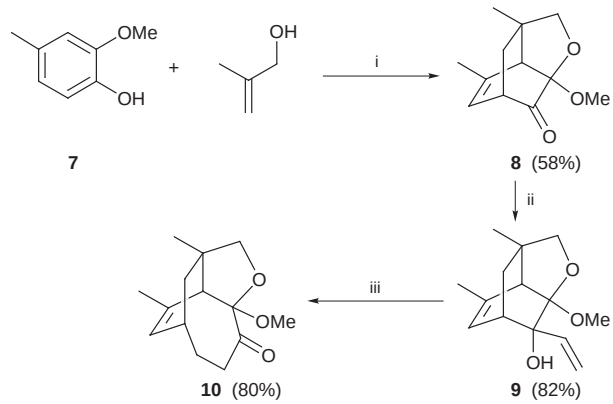
1 **2**

The synthesis of the bicyclo[4.2.2]decane skeleton poses a considerable challenge. Although a few methods exist for their synthesis,[2,3] they lack versatility and provide the desired skeleton only after several steps. Despite the long sequence of reactions it requires, Uyehara's approach to this skelecton is noteworthy.[2] Quite recently, we have developed a novel and efficient four-step methodology starting from 2-methoxyphenols, *via* anionic [1,3]-rearrangement of vinylbicyclo[2.2.2]-octenol derivatives as the key step, for the stereocontrolled synthesis of functionalized bicyclo[4.2.2]decenones (Scheme 1).[4] We herein report the first total synthesis of (±)-**1** clearly expressing the utility of the aforementioned methodology.

It was planned to use compound **10** as the key intermediate to achieve the synthesis of **1**, as we expected compound **9** to undergo anionic [1,3]-rearrangement. Synthesis of compound **10** was accomplished as shown in Scheme 2. Accordingly, the



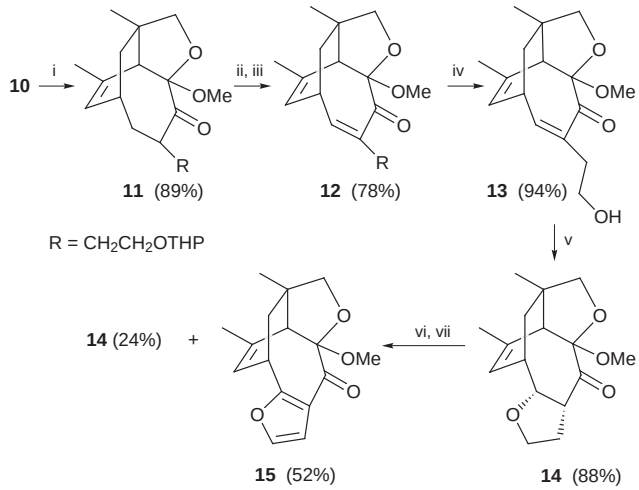
Scheme 1 *Reagents and conditions*: i, allyl alcohol, $PhI(OAc)_2$, CH_2Cl_2; ii, CH_2=CHMgBr; iii, KH, 18-crown-6.



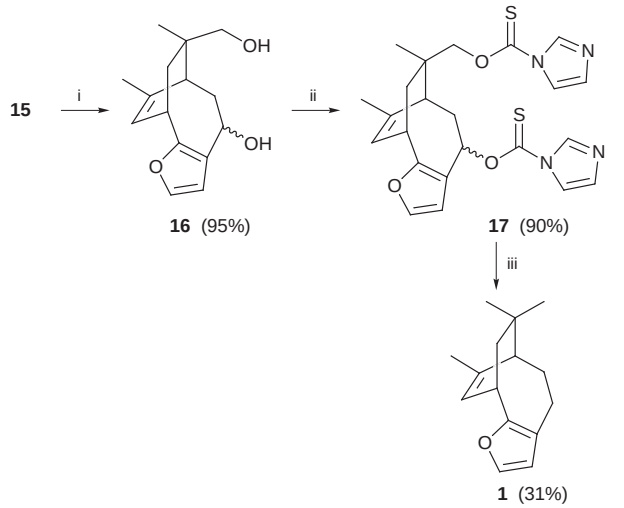
Scheme 2 *Reagents and conditions*: i, $PhI(OAc)_2$, $NaHCO_3$, 55–60 °C; ii, CH_2=CHMgBr, $ZnBr_2$, −78 °C to room temp.; iii, KH, 18-crown-6, 1,4-dioxane, reflux.

requisite bicyclo[2.2.2]octenone derivative **8** was prepared from 2-methoxy-4-methylphenol **7** in 58% yield, following a procedure developed in our laboratory for the synthesis of similar compounds.[5] Stereoselective addition of vinylmagnesium bromide to compound **8** in the presence of zinc bromide at −78 °C afforded **9** in 82% yield as the only discernible product. Subsequent anionic [1,3]-rearrangement of **9** proceeded smoothly to provide **10** in 80% yield (Scheme 2).

With compound **10** in hand, the stage is set for the construction of the furan ring, which was accomplished *via* seven synthetic steps, as shown in Scheme 3. The required two-carbon unit was introduced *via* alkylation of **10** using 1-bromo-2-(2-tetrahydropyranyloxy)ethane in the presence of KH at 0 °C in THF to obtain compound **11** in 89% yield as a 1:1 mixture of diastereomers. Then compound **11** was converted into the corresponding enone **12** using Saegusa's procedure[6] in two steps and in about 78% yield. The removal of the THP group was achieved *via* transacetalization with Pr^{i}OH catalyzed by PPTS to obtain the alcohol **13** as a single product. Intra-



Scheme 3 *Reagents and conditions*: i, RBr, KH, THF, 0 °C; ii, KH, TMSCl; iii, $Pd(OAc)_2$, MeCN; iv, Pr^{i}OH, PPTS, 55 °C; v, NaOH, MeOH, 80 °C; vi, KH, TMSCl; vii, DDQ, benzene, reflux.



Scheme 4 *Reagents and conditions*: i, SmI_2, MeOH, THF; ii, 1,1′-thiocarbonyldiimidazole, $ClCH_2CH_2Cl$, reflux; iii, Bu_3SnH, AIBN, toluene, reflux.

molecular Michael addition of **13** by treatment with 6 M aq. NaOH in MeOH at 80 °C furnished the tetrahydrofuran **14** as a single stereoisomer in 88% yield. The assigned stereochemistry of compound **14** was based on NOE experiments. Aromatization of **14** was accomplished *via* treatment of its silyl enol ether (KH, TMSCl) with DDQ in refluxing benzene to obtain the desired compound **15** in 52% yield, along with 24% of **14** (Scheme 3).

With construction of the complete carbon framework of **1** accomplished, the remaining task was to deoxygenate **15**. Towards this end, reduction of **15** with SmI_2 in the presence of MeOH was carried out first to obtain the diols **16** as a mixture of epimers,[7] which were converted then into a mixture of the corresponding bis-thiocarbamates **17** in 90% yield. The last hurdle to target compound **1** was passed by means of reduction of **17** with tin hydride initiated by AIBN in refluxing toluene (Scheme 4).[8] The structure of **1** was unambiguously established by its IR, ^1H and ^{13}C NMR, low and high resolution mass spectral data.[9] The UV, ^1H NMR and mass spectral data of synthetic (±)-**1** were found to be essentially identical with those reported by Cimino *et al*. for the natural product.[1]

Thus the synthesis of (±)-**1** was accomplished in 13 steps from readily available starting materials. In conclusion, the synthesis of (±)-**1** described here clearly exhibits the versatility of our methodology for the construction of the bicyclo[4.2.2]-decane skeleton and also confirms the structural assignments of the natural product.

The authors thank the National Science Council of the Republic of China for the financial support of this research work. We also thank Dr P. Dharma Rao for helpful discussions.

Notes and references

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9 *Selected data* for synthetic **1**: ν_{max}(neat)/cm^{-1} 2922 (s), 1505 (m), 1439 (m); δ_H(400MHz, $CDCl_3$) 7.07 (d, *J* 1.6, 1H), 6.03 (d, *J* 1.6, 1H), 5.81 (dq, *J* 6.9, 1.2, 1H), 3.43 (ddd, *J* 6.9, 6.6, 2.4, 1H), 2.36–2.28 (m, 1H), 2.21–2.04 (m, 3H), 1.92–1.84 (m, 1H), 1.60–1.53 (m, 2H), 1.79 (d, *J* 1.2, 3H), 0.91 (s, 3H), 0.77 (s, 3H); δ_C(100 MHz, $CDCl_3$) 153.2 (C), 141.2 (C), 138.0 (CH), 120.7 (CH), 118.1 (C), 113.5 (CH), 50.1 (CH), 43.8 (CH_2), 36.7 (CH_3), 33.8 (CH), 33.5 (C), 30.5 (CH_2), 29.9 (CH_3), 23.6 (CH_3), 22.0 (CH_2); *m/z* (70 eV) 216 (M^+); HRMS (EI): Calc. for $C_{15}H_{20}O$: 216.1514; found : 216.1504.

Communication 8/08714H