The first total synthesis of (±)-pallescensin B

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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\(^2\).

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 skeleton is noteworthy.\(^2\) Quite recently, we have developed a novel and efficient four-step methodology starting 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 \(-78^\circ\text{C}\) 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 \(0^\circ\text{C}\) 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. Intrare...
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, 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). The structure of 1 was unambiguously established by its IR, $^1$H and $^{13}$C NMR, low and high resolution mass spectral data. The UV, $^1$H 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.

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.

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Notes and references

9 Selected data for synthetic 1: $\nu_{max}$(neat)/cm$^{-1}$ 2922 (s), 1505 (m), 1439 (m); $\delta_H$(400MHz, CDCl$_3$) 7.07 (d, $J$ 1.6, 1H), 6.03 (d, $J$ 1.6, 1H), 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.

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