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A Non-Photochemical Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin

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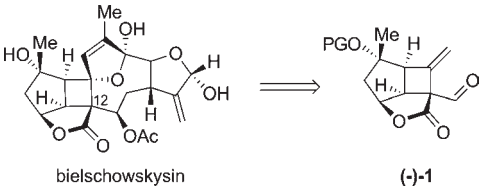
ABSTRACT



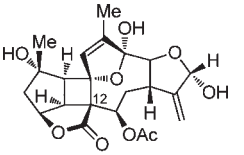
bielschowskysin (-)-1

An asymmetric synthesis of the tricyclic core (−)-1 of the marine diterpene bielschowskysin is described. In particular, a methodology was developed to introduce the crucial quaternary center at C-12.

In 2004, Rodriguez et al.[1] reported the isolation of the highly oxygenated diterpene bielschowskysin (Figure 1) from the gorgonian octacoral *Pseudopterogorgia kallos*, found in the Southwestern Caribbean Sea. Its strong antimalarial activity and significant cytotoxicity against lung and renal cancer cell lines as well as its unique *cis*-fused tricyclo[9.3.0.0^{2,10}]tetradecane ring system including 11 stereocenters immediately caught the attention of the scientific community.

Since its structural elucidation, three efforts toward the total synthesis of the diterpenoid have been reported, all of which are centered around a biomimetic intramolecular [2 + 2]-photocycloaddition to create the crucial [4,5]-core fragment (Scheme 1).[2−4] In none of these approaches, however, could the quaternary center at C-12 be established. This appears to be a major drawback, as due to Bredt's rule, this position is deactivated in a structure such as **I** toward the formation of the enolate **II** required for the addition of an appendage, for instance via aldol addition (Scheme 2).

An obvious way to generate the appropriate functionality is the intramolecular [2 + 2]-photocyclization of **III** to **IV**.



bielschowskysin

Figure 1. Structure of bielschowskysin.

However, despite extensive variation of substituents and conditions, the desired product was not obtained.

Hence, we report a stereoselective nonphotochemical synthesis of the fully substituted core fragment **(−)-1** of bielschowskysin including its all-carbon quaternary center from the known optically active alcohol **(+)-4**, which was obtained in a four-step sequence starting from commercially available **rac-2** (Scheme 3).[5]

Our synthesis started with a TBS-protection of **(+)-4** to furnish **(−)-5**. To functionalize the five-membered ring, photooxygenation[6] with molecular oxygen in the presence of acetic anhydride and base was chosen. This oxidation was exceptionally easy to carry out, even on a molar scale,

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(2) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906.
(3) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731–1733.
(4) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5149–5152.

(5) (a) Gaich, T; Weinstabl, H; Mulzer, J. *Synlett* **2009**, *9*, 1357–1366. (b) Weinstabl, H. Ph.D. Thesis, University of Vienna, 2011.
(6) Mihelich, E. D.; Eickhoff, D. J. *J. Org. Chem.* **1983**, *48*, 4135–4137.

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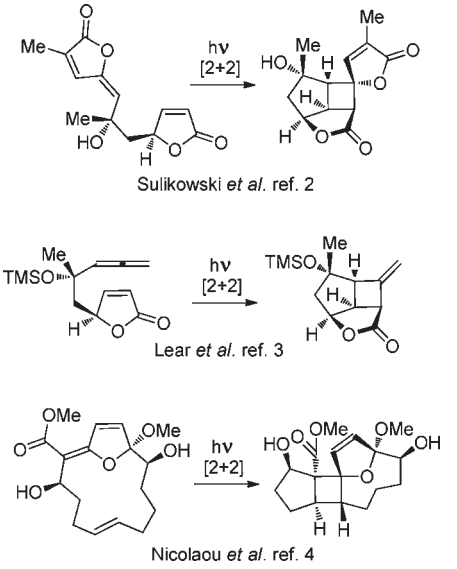
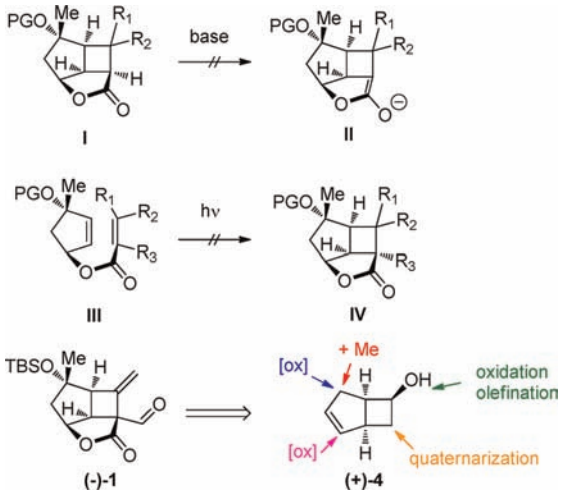
Scheme 1. Previously Reported [2 + 2] Photocycloadditions



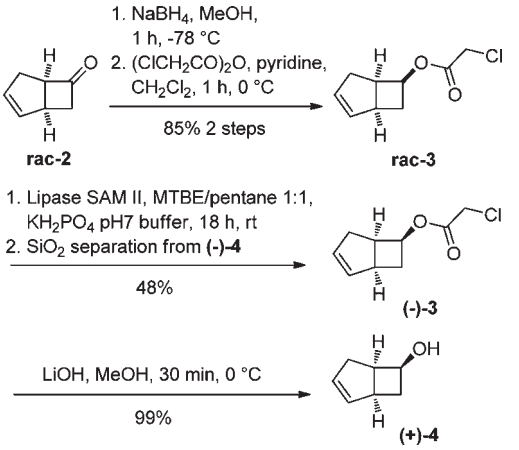
Scheme 2. Retrosynthetic Analysis



and produced the α,β-unsaturated ketone **(−)-6** with high regioselectivity (dr = 20:1). Conjugate addition with dimethyl cuprate, trapping of the enolate with TMSOTf to give enol ether **(−)-7**, and Saegusa−Ito oxidation[7] provided ketone **(−)-9**. The success of the Saegusa oxidation crucially depended on the use of DMSO as solvent and molecular oxygen as cooxidant. Otherwise, the reaction was difficult to scale up, suffered from inconsistent yields, and TMS-enol ether **(−)-7** was prone to desilylation to form undesired ketone **(−)-8** (Scheme 4).

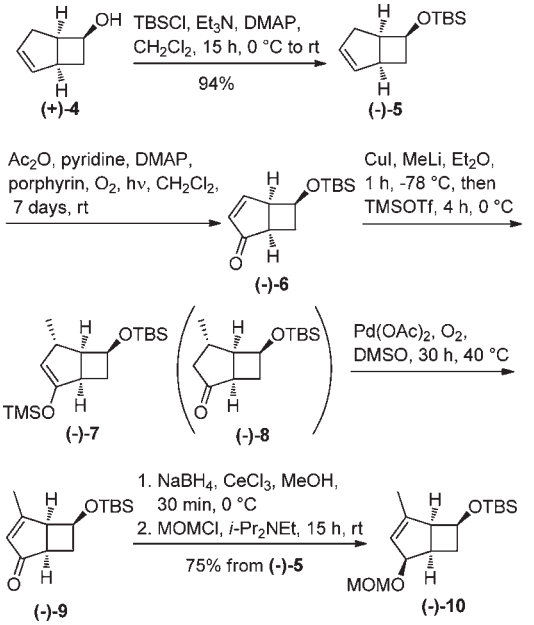
Taking advantage of the "open-book" geometry of bicycle **(−)-9**, the carbonyl group was reduced diastereoselectively under Luche conditions.[8] MOM-protection yielded diol

Scheme 3. Preparation of Optically Pure Starting Material



derivative **(−)-10**. The sequence could be carried out in 75% overall yield from **(−)-5** without purification of intermediates. Molecular oxygen, a catalytic amount of cobalt complex, and phenylsilane promoted the Mukaiyama−Isayama oxidation−reduction−hydration[9] in a regio- and stereoselective manner, leading to tertiary alcohol **(−)-11**.

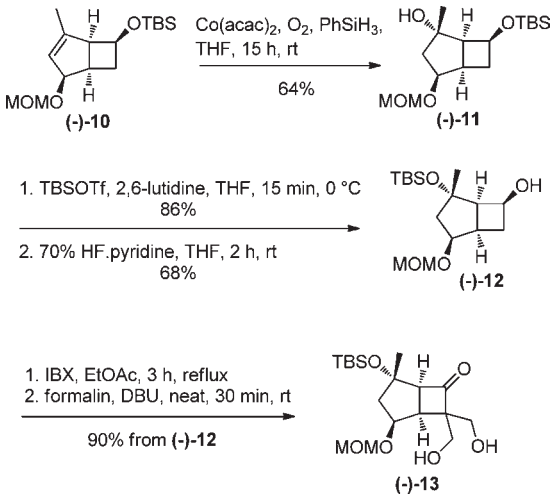
Scheme 4. Functionalization of the Five-Membered Ring



After a protection−deprotection sequence, the five-membered ring in bicycle **(−)-12** was appropriately substituted, and the installation of the quaternary center could be envisaged (Scheme 5). In effect, IBX oxidation smoothly established the ketone, which underwent double aldol reaction with formalin to deliver key intermediate **(−)-13**.

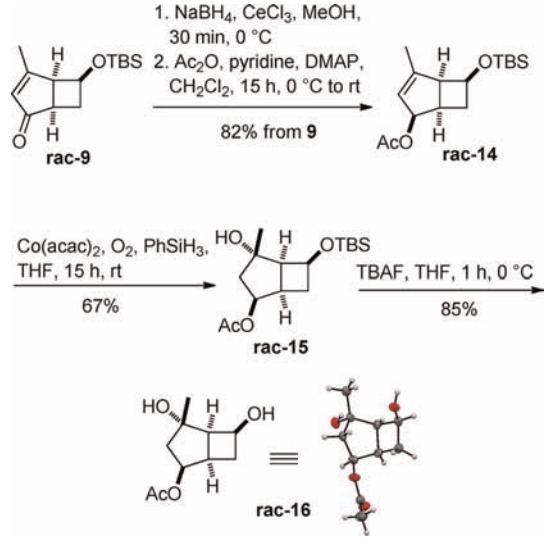
(7) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013.
(8) Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.
(9) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 1071–1074.

Scheme 5. Quaternarization of the Bicycle



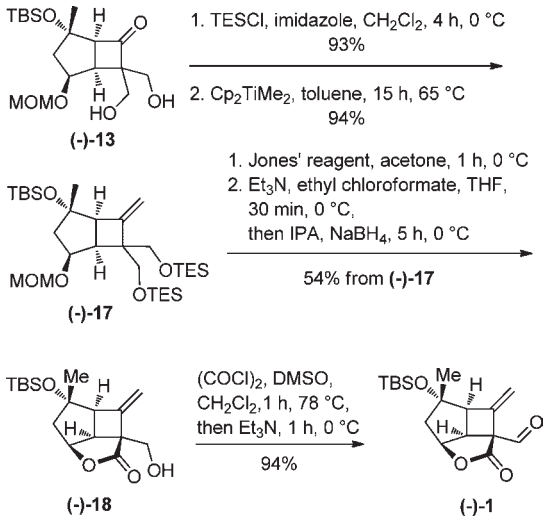
To establish the stereochemical course of the hydration, crystalline diol **16** was prepared via an analogous sequence and subjected to single crystal X-ray diffraction. In this way, it was confirmed that the oxygen indeed attacks the bicyclic olefin from the less hindered convex face, as expected (Scheme 6).

Scheme 6. Preparation of Single Crystals for X-ray Analysis



Our synthesis was continued with the TES-protection of the two primary alcohols (Scheme 7). Ketone olefination using Petasis' reagent generated **(−)-17** in excellent yield. Next, a cascade reaction was used to create the tricyclic core of bielschowskysin. Under the acidic conditions of Jones' reagent, the diol was formed in situ and oxidized to

Scheme 7. Formation of the Tricycle



the dicarboxylic acid. Concomitantly, the MOM protecting group was removed, whereupon lactonization occurred spontaneously. Without purification, the crude carboxylic acid was selectively reduced via a mixed carbonate formed from ethyl chloroformate. Final purification delivered alcohol **(−)-18** in 54% overall yield after a total of eight transformations (> 92% each) from **(−)-17**. Swern oxidation eventually furnished the targeted aldehyde **(−)-1**.

In conclusion, we have developed a fully stereoselective scalable route (11% overall yield from known alcohol **(+)-4**) to a tricyclic core fragment of bielschowskysin which, for the first time, contains the all-carbon quaternary center at C-12. The aldehyde function in **(−)-1** is well suited for attaching the eastern part of the molecule and this is well underway in our laboratory. Apart from this, the regio- and stereocontrolled functionalization of the versatile and readily available precursor **4** may be of interest in other synthetic projects.

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Supporting Information Available. Experimental procedure and full characterization including copies of ^{1}H and ^{13}C NMR spectra and crystal structure analysis of **rac-16** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.