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Stereocontrolled approach to the highly functionalized bicyclo[3.2.0] heptane core of bielschowskysin through intramolecular Cu(I)-catalyzed [2+2] photocycloaddition

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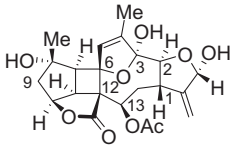
ABSTRACT

A direct route for the synthesis of highly functionalized bicyclo[3.2.0]heptane core containing the bridged lactone with the functionalized C-12 substituent of bielschowskysin is reported. The key step involves a stereoselective Cu (I)-catalyzed [2+2] photocycloaddition of a 1,6-diene embedded in a sugar derivative.

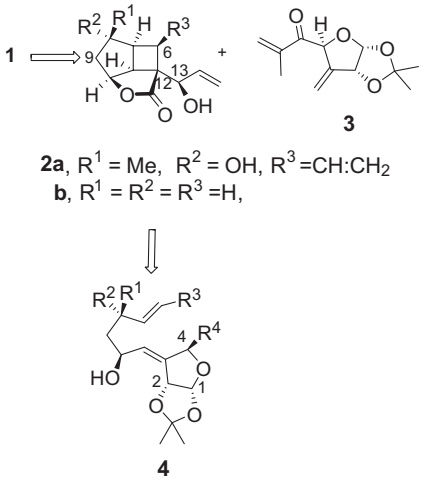
The marine diterpene bielschowskysin **1**[1] isolated from Caribbean gorgonian octocoral *Pseudopterogorgia kallos* possesses a highly oxygenated unprecedented novel [9.3.0.0[2,10]] tetradecane ring system. Seven of the eleven stereocenters present in it are contiguous, six of which reside on the periphery of the bicyclo[3.2.0]heptane unit. It exhibits antiplasmodium activity against *Plasmodium falciparum* and strong cytotoxicity against human lung cancer and renal cancer cell lines.[1] Structural complexity combined with its strong bioactivity profile, bielschowskysin elicited considerable interest[2] for developing synthetic strategies. Global growing interest on synthetic approaches prompted us to report preliminary results of our investigation leading to a stereocontrolled route to the construction of highly functionalized bicyclo[3.2.0]heptane unit with the bridged lactone present in **1**.



1 : Bielschowskysin

We envisaged that coupling of the prebuilt bicyclo[3.2.0] heptane unit **2a** with the fragment **3** would be a feasible route to **1** (Scheme 1).

A major problem in the synthesis of **1** lies in the creation of bridge head quaternary center (C-12) with a stereodefined hydroxyl group at C-13. A few approaches have been reported in the literature for the synthesis of the bicyclo[3.2.0]heptane unit of **1**. However, some[2a,b] of the bicyclo[3.2.0]heptane derivatives synthesized so far lack the C-12 appendage and will require an unfavorable aldol reaction at the bridge head lactone enolate for its attachment while the other ones[2d] will require chemo-and



Scheme 1.

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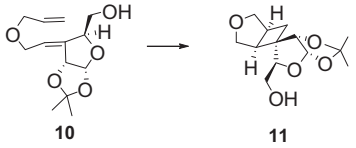
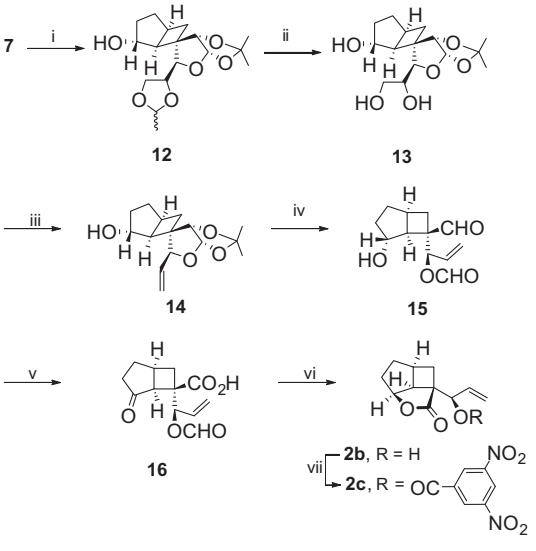
stereoselective nucleophilic addition to an aldehyde carbonyl at C-13 for elaboration to **1**. Thus the reported approaches have limitations in generating C-12 quaternary center and the C-13 acetoxy group. We initially focused on designing a route to construct a bicyclo[3.2.0]heptane derivative containing the bridged lactone with the C-12 appendage with simultaneous generation of the C-13 OH group without employing the unfavorable aldol reaction at the bridge head lactone enolate. We speculated that an intramolecular Cu (I)-catalyzed [2+2] photocycloddition[3] in the sugar embedded diene **4** will set the stage for stereoselective[4–6] generation of the bicyclo[3.2.0]heptane core with appropriately functionalized substituents (C-12, C-13 of **1**) in a single step. The C-1, C-2 sector of the glucose moiety in **4** is a latent carboxylic acid which can be employed to construct the lactone unit while C-4 oxygen of the sugar ring will provide the C-13 acetoxy group of **1**. Use of glucose will also provide the target in an enantiomerically pure form. Realization of this concept is demonstrated here with the synthesis of the bicyclo[3.2.0]heptane derivative **2b**.

We initially chose the diene **7** to demonstrate the feasibility of the photocycloaddition event for accessing stereoselectively the bicyclo[3.2.0]heptane core. The aldehyde **6** prepared from oxidation of the known hydroxy-compound **5**[5] with Dess–Martin periodinane (DMP) was allowed to react with 1-butenyl-4-magnesium bromide to provide the diene **7**[7] along with its other diastereomer in ca. 4:1 ratio in 82% yield (Scheme 2). The diene **7** was isolated in 65% yield as the major diastereoisomer by column chromatography. The stereochemical assignment to the newly generated stereocenter follows from addition of the Grignard reagent from the face opposite to the 1,2-acetonide moiety. The diacetonide **7** was then transformed into diene **8** in 70% overall yield through a three-step protocol involving selective deprotection of 5,6-acetonide moiety-periodate cleavage of the resulting vicinal diol followed by reduction of the aldehyde. When a solution of the diene **8** in diethyl ether was irradiated with a 450 W Hanovia medium pressure mercury vapor lamp through a water cooled quartz immersion well in the presence of $2CuOTf.C_6H_6$ complex as catalyst for 3 h, the cyclobutane derivative **9** was obtained in 75% yield (Scheme 2). The relative stereochemistry of the newly generated stereocenters was established by comparison of the coupling constant of the hydrogen α to the hydroxyl group with that reported in the literature. The coupling constant (J = 3 Hz) observed for **9** is closely comparable with that reported[4] (J = 4 Hz) for hydrogen α to the hydroxyl group in exo-2-hydroxy bicyclo[3.2.0]heptane and not with that (J = 8 Hz) reported for the corresponding endo-hydroxy analogue. Thus the hydrogen α to the hydroxyl group was assigned as *anti* to the ring junction hydrogens. That the cycloaddition took place from the face opposite to the 1,2-acetonide moiety was based on analogy[6] to the formation of the adduct **11** from photocycloaddition of the structurally analogous diene **10**.

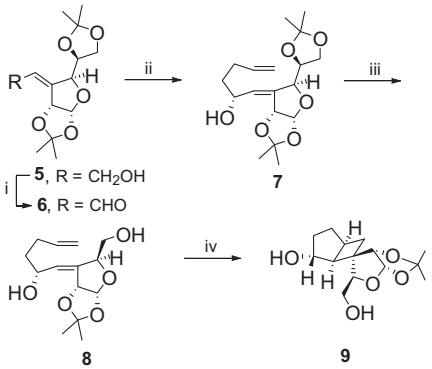


The synthesis of the bicyclo[3.2.0] heptane derivative **2b** is shown in Scheme 3. Photocycloaddition of the diene **7** in the presence of CuOTf as catalyst gave the cyclobutane derivative **12** in 65% yield as a mixture of two diastereoisomers arising from transformation[8] of the acetonide moiety of **7** to the acetal unit in **12**. The relatively less crowded 5,6-acetal unit compared to the 1,2-acetonide unit of the glucofuranose moiety in **12** was selectively[9] removed on treatment with a catalytic amount of DDQ to afford the cyclobutane derivative **13** as a single diastereoisomer demonstrating that **12** was a diastereoisomeric mixture due to the presence of the C-5, C-6 acetal. The coupling constant (J = 3.3 Hz) of the hydrogen α to the hydroxyl group confirmed the relative stereochemistry of the hydroxy-bicyclo[3.2.0]heptane unit in **13**. After establishing the stereochemical outcome in the photocycloaddition, we proceeded for the synthesis of the targeted intermediate **2b** employing the photoadduct **12**.

Cleavage of the vicinal diol in **13** with $NaIO_4$ followed by Wittig olefination of the resulting aldehyde produced the alkene **14** in 65% overall yield. A three dimensional view generated by Chemdraw 3D reveals that the C-10 hydroxyl group is *anti* to the bond linking the acetonide moiety. Thus an inversion of the configuration of the C-10 hydroxyl group is required for lactonization with the carboxylic acid to be generated from the acetonide moiety. For this purpose an oxidation–reduction sequence was employed as delineated in Scheme 3. Treatment of **14** with 4% aqueous H_2SO_4 followed by periodate cleavage of the resulting diol afforded the hydroxy-aldehyde **15** in 80% yield. Treatment of the



Scheme 3. Reagents and conditions: (i) hυ, CuOTf, Et_2O, 3 h, 65%; (ii) DDQ, CH_3CN-H_2O, 65 °C, 2 h, 88%; (iii) (a) $NaIO_4$, THF-H_2O, 0 °C, 1.5 h; (b) Ph_3PCH_3Br, KHMDS, THF, −10 °C, 2 h; 65% from 13; (iv) (a) H_2SO_4, dioxane, 80 °C, 2 h; (b) $NaIO_4$, THF-H_2O, 0 °C, 1.5 h, 80% from 14; (v) Jones' reagent, acetone, 0 °C, 30 min, 88%; (vi) $NaBH_4$, MeOH, HCl, 0 °C to rt, 1.5 h, 91%; (vii) 3,5-dinitrobezoyl chloride, CH_2Cl_2, Et_3N, DMAP, rt, 5 min, 71%.



Scheme 2. Reagents and conditions: (i) DMP, CH_2Cl_2, 0 °C, 1 h, 96%; (ii) CH_2:$CHCH_2CH_2Br$, Mg, THF, 0 °C, 1 h, 65%; (iii) (a) AcOH-H_2O(4:1), rt; (b) $NaIO_4$, THF-H_2O, 0 °C, 1.5 h; (c) $LiAlH_4$, Et_2O, 0 °C, 1.5 h, 70% from 7; (iv) hυ, CuOTf, Et_2O, 2 h, 75%.

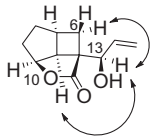


Figure 1. NOESY for **2b**.

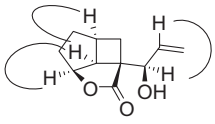


Figure 2. COSY for **2b**.

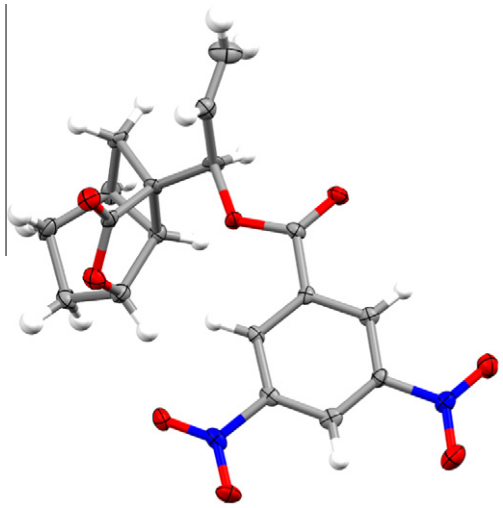


Figure 3. ORTEP diagram of compound **2c**.

hydroxy-aldehyde **15** with Jones' reagent afforded the keto-acid **16** in ca. 88% yield. The rapidly decomposing formate in **16** (as revealed by ^{1}H and ^{13}C NMR) led us to use the crude acid without further purification for reduction of the carbonyl group. Treatment of the keto-acid **16** with sodium borohydride followed the well established trend[4] of hydride addition from the least hindered exo face of the bicyclo[3.2.0]heptane moiety resulting in the inversion of configuration of the C-10 OH group which underwent spontaneous lactonization to afford directly the bridged γ-butyrolactone **2b** in 85% yield. The coupling constant (J = 5 Hz) observed for the C-10 H is closely comparable to that reported for endo-2-hydroxy bicyclo[3.2.0]heptanes. This established that C-10 H is *syn* to the ring fusion H's as required for **1**. Additional support in favor of the stereochemical assignment to **2b** was obtained with the aid of 2D NMR spectroscopy (COSY, NOESY, and HSQC). Strong correlation was observed between C-13 H and C-11 H as well as between C-13 H with C-6 H in NOESY (Fig. 1). In COSY spectra (Fig. 2), strong correlations were noted between the following pairs-C-7/C-11 H's, C-10/C-11 H's, and C-13/C-14 H's. Finally, the structure of **2b** was confirmed by single crystal X-ray (Fig. 3)[10] of its 3,5-dinitrobenzoate derivative **2c**.

In conclusion, we have developed a stereocontrolled route to a bicyclo[3.2.0]heptane core with the bridge head lactone with the C-12 appendage present in bielschowskysin **1**. The attractive feature of this route is that it directly provides the bicyclo[3.2.0]heptane moiety with stereoselective generation of the C-12 quaternary center with stereodefined C-13 hydroxyl group through an intramolecular stereoselective Cu(I)-catalyzed [2+2] photocycloaddition of 1,6-diene embedded in a sugar derivative.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.018.

References and notes

1. Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661.
2. (a) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903; (b) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731; (c) Nicolaou, K. C.; Adsool, V. A.; Hale, R. H. *Angew. Chem. Int. Ed.* **2011**, *50*, 5149; (d) Farcet, J. B.; Himmelbauer, M.; Mulzer, J. *Org. Lett.* **2012**, *14*, 2195.
3. For reviews on intramolecular Cu(I)-catalyzed [2+2] photocycloaddition of 1,6-dienes see: (a) Salomon, R. G. *Tetrahedron* **1983**, *39*, 485; (b) Ghosh, S. In *CRC Hand Book of Organic Photochemistry and Photobiology*; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, Florida, 2004. Chapter 18.
4. Salomon, R. G.; Coughlin, D. J.; Ghosh, S.; Zagorski, M. G. *J. Am. Chem. Soc.* **1982**, *104*, 998.
5. (a) Patra, D.; Ghosh, S. *J. Org. Chem.* **1995**, *60*, 2526; (b) Ghosh, S.; Patra, D.; Samajdar, S. *Tetrahedron Lett.* **1996**, *37*, 2073; (c) Holt, D. J.; Barker, W.; Jenkins, P. R.; Ghosh, S.; Russell, D. R.; Fawcett, J. *Synlett* **1999**, 1003; (d) Bannerjee, S.; Ghosh, S. *J. Org. Chem.* **2003**, *68*, 3981; (e) Sarkar, N.; Nayek, A.; Ghosh, S. *Org. Lett.* **2004**, *6*, 1903.
6. Mondal, S.; Yadav, R. N.; Ghosh, S. *Org. Biomol. Chem.* **2011**, *9*, 4903.
7. All new compounds were characterized through spectroscopic data. Physical characteristics for selected compounds: Compound **8**. $[\alpha]_D^{25}$ +131.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (1H, d, J = 4.5 Hz), 5.87–5.79 (1H, m), 5.61 (1H, d, J = 8.0 Hz), 5.23 (1H, d, J = 4.0 Hz), 5.04 (1H, dd, J = 1.5, 17.5 Hz), 4.98 (1H, d, J = 10.0 Hz), 4.84 (1H, s), 4.46 (1H, q, J = 7.0 Hz) 3.80 (1H, dd, J = 3.0, 12.3 Hz), 3.59 (1H, dd, J = 4.5, 11.8 Hz), 2.19 -2.07 (2H, m), 1.98 (2H, br s), 1.80–1.73 (1H, m), 1.67–1.60 (1H, m), 1.49 (3H, s), 1.40 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.1 (C), 138.1 (CH), 130.6 (CH), 115.2 (CH_2), 112.6 (C), 105.1 (OCHO), 81.2 (OCH), 78.9 (OCH), 69.0 (OCH), 64.5 (OCH_2), 35.8 (CH_2), 29.7 (CH_2), 27.7 (CH_3), 27.6 (CH_3); HRMS (ESI) m/z Calcd for $C_{14}H_{22}O_5Na$ (M+Na)$^+$, 293.1365; found, 293.1366. Compound **9**. $[\alpha]_D^{25}$ +52.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (1H, d, J = 3.5 Hz), 4.62 (1H, d, J = 4.0 Hz), 4.27 (1H, d, J = 3.0 Hz), 4.12–4.08 (1H, m), 3.97–3.88 (2H, m), 2.90–2.65 (2H, br s), 2.71 (1H, t, J = 7.5 Hz), 2.40 (1H, d, J = 7.0 Hz), 2.13–2.09 (2H, m), 2.02–1.97 (1H, m), 1.93–1.86 (2H, m), 1.48 (3H, s), 1.28 (3H, s) 1.08 (1H, dd, J = 6.5, 13.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 112.3 (C), 104.0 (OCHO), 86.1 (OCH), 83.6 (OCH), 74.7 (OCH), 61.7 (OCH_2), 49.3 (CH), 46.1 (C), 34.5 (CH), 33.6 (CH_2), 30.1 (CH_2), 27.9 (CH_2), 26.9 (CH_3), 26.5 (CH_3); HRMS (ESI) m/z Calcd for $C_{14}H_{22}O_5Na$ (M+Na)$^+$, 293.1365; found, 293.1365. Compound **14**. $[\alpha]_D^{27}$ +65.8 (*c* 2.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.00 (1H, ddd, J = 6.4, 10.7, 17.1 Hz), 5.65 (1H, d, J = 3.5 Hz), 5.48 (1H, dt, J = 1.5, 17.2 Hz), 5.36 (1H, dt, J = 1.4, 10.6 Hz), 4.65 (1H, d, J = 4.1 Hz), 4.43 (1H, d, J = 6.2 Hz), 4.32 (1H, d, J = 3.5 Hz), 2.63–2.57 (1H, m), 2.29 (1H, d, J = 6.8 Hz), 2.09–2.00 (2H, m), 1.94–1.83 (2H, m), 1.67 (1H, br s), 1.49 (3H, s), 1.49–1.42 (1H, m), 1.30 (3H, s), 1.08 (1H, dd, J = 6.3, 9.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.6 (CH), 119.2 (CH_2), 112.1 (C), 104.0 (OCHO), 85.5 (OCH), 83.7 (OCH), 75.0 (OCH), 49.3 (CH), 47.7 (C), 34.9 (CH_2), 33.2 (CH), 30.0 (CH_2), 28.0 (CH_2), 26.9 (CH_3), 26.5 (CH_3); HRMS (ESI) m/z Calcd for $C_{15}H_{22}O_4Na$ (M+Na)$^+$, 289.1416; found, 289.1414. Compound **2b**. $[\alpha]_D^{27}$ −53.9 (*c* 0.56, $CHCl_3$); υ_{max} (neat) 3445, 2926, 1746 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (1H, ddd, J = 6.5, 10.5, 17.0 Hz), 5.42 (1H, d, J = 17.5 Hz), 5.30 (1H, d, J = 10.5 Hz), 5.00 (1H, t, J = 5.0 Hz), 4.34 (1H, d, J = 6.0 Hz), 3.18 (1H, t, J = 7.5 Hz), 2.75 (1H, dd, J = 9.5, 11.0 Hz), 2.70–2.63 (1H, m), 2.27 (1H, dd, J = 6.5, 10.0 Hz), 2.20–2.13 (2H, m), 1.87–1.60 (2H, m), 1.27–1.24 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1 (CO), 135.2 (CH), 118.3 (CH_2), 85.3 (OCH), 72.7 (CHO), 49.4 (C), 45.8 (CH), 36.3 (CH_2), 32.6 (CH), 32.2 (CH_2), 31.3 (CH_2); HRMS (ESI) m/z Calcd for $C_{11}H_{14}O_3Na$ (M+Na)$^+$, 217.0841; found, 217.0842.
8. Mondal, S.; Yadav, R. N.; Ghosh, S. *Tetrahedron Lett.* **2010**, *51*, 4452.
9. Fernàndez, J. M. G.; Mellet, C. O.; Mañin, A. M.; Fuentes, J. *Carbohydr. Res.* **1995**, *274*, 263.
10. Crystal data: Compound **2c**. Colorless, needle shaped crystal. Empirical formula $C_{18}H_{16}N_2O_8$, M_r = 388.33, Orthorhombic space group $P2_12_12_1$, a = 5.830 (3), b = 9.556 (4), c = 31.119 (14) Å, v = 1733.7 (14) Å^3, z = 4, T = 150 K,

ρ_{calcd} = 1.488 g cm^{-3}, $F(000)$ = 808.0, λ (Mo-Kα) = 0.71073 Å, μmm^{-1} = 0.119, $2\theta_{max}$ = 50.0°, 4171 total reflections, 2858 unique reflections, 1802 observed ($I > 2\sigma(I)$), 253 refined parameter, R_1 = 0.0596, wR_2 = 0.1866, with GOF = 0.999. X-ray single crystal data were collected using MoKα (λ = 0.7107 Å) radiation on a SMART APEX II diffractometer equipped with CCD area detector. Data collection, data reduction, and structure solution/refinement were carried out using the software package of SMART APEX. The structure was solved by the direct method and refined in a routine manner. Non hydrogen atoms were treated anisotropically. The hydrogen atoms were geometrically fixed. CCDC (CCDC No. 902058 for **2c**) contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223 336 033; or deposit@ccdc.cam.ac.uk.