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A Palladium-Catalyzed Carbo-oxygenation: The Bielschowskysin Case

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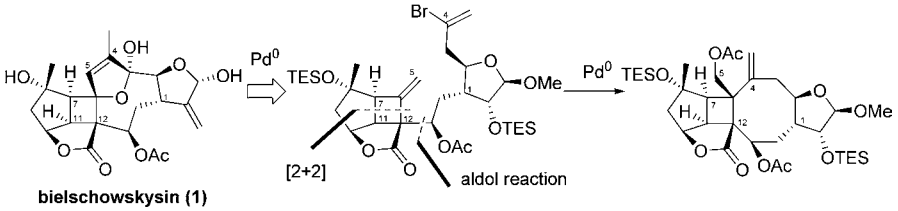
ABSTRACT



An asymmetric synthesis of an advanced tetracyclic intermediate toward the synthesis of bielschowskysin (1) is described. A biomimetic [2 + 2]-photocyclization was used to establish the cyclobutane core of bielschowskysin. Macrocyclization under Heck conditions led to an unprecedented carbo-oxygenation of a 1,1-disubstituted double bond.

Over the past years the Rodríguez group has reported the isolation of a stunning variety of terpenoids from the Caribbean Sea plume *Pseudopterogorgia kallos*, among which bielschowskysin (**1**)[1] (Scheme 1) has attracted an unusual amount of interest.

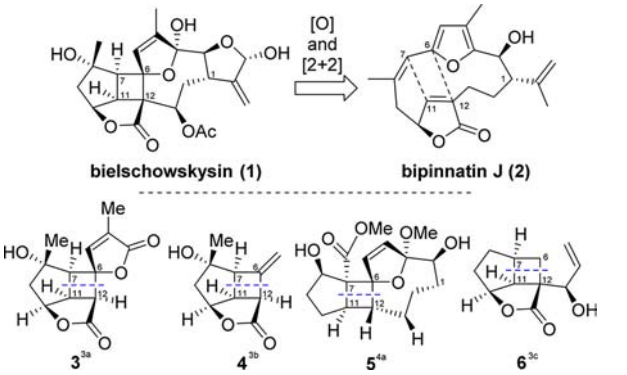
Partly this is due to its significant antiplasmodial activity against the malaria causing protozoan parasite *Plasmodium falciparum* and its cytotoxic activity against two human cancer cell lines. Most significantly, its densely functionalized polycyclic diterpenoid structure including an unprecedented tricyclo[9.3.0.0^{2,10}]-tetradecane ring system and 11 stereogenic centers has rendered bielschowskysin a highly competitive target in synthetic chemistry.

So far, activities from numerous research groups, including our own,[2] have resulted in several advanced intermediates[3] and test systems.[4]

According to the studies by Roethle and Trauner the biosynthesis of different furanocembranoids could be related to bipinnatin J (**2**) and should therefore be accessible from this natural product within a short number of steps including oxidations, rearrangements, and cycloadditions.[5,6] In particular, it is proposed that epoxidation of the $\Delta^{7,8}$ double bond of bipinnatin J (**2**) followed by the addition of water and a consecutive formal [2 + 2]-cycloaddition could lead to bielschowskysin (Scheme 1).

To date this biomimetic [2 + 2]-photocycloaddition strategy has been pursued by four groups. However, the

Scheme 1. Biosynthesis and Reported [2 + 2]-Approaches



(1) Marrero, J.; Rodríguez, A. D.; Baran, P.; Raptis, R. G.; Sanchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett.* **2004**, *6*, 1661–1664.

(2) (a) Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Org. Lett.* **2012**, *14*, 2195–2197. (b) Farcet, J.-B.; Himmelbauer, M.; Mulzer, J. *Eur. J. Org. Chem.* **2013**accepted for publication.

(3) (a) Doroh, B.; Sulikowski, G. A. *Org. Lett.* **2006**, *8*, 903–906. (b) Miao, R.; Gramani, S. G.; Lear, M. J. *Tetrahedron Lett.* **2009**, *50*, 1731–1733. (c) Jana, A.; Mondal, S.; Md. Hossain, F.; Ghosh, S. *Tetrahedron Lett.* **2012**, *53*, 6830–6833.

(4) (a) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 5149–5152. (b) Meyer, M. E.; Phillips, J. H.; Ferreira, E. M.; Stoltz, B. M. *Tetrahedron* **2013**, 1–9.

(5) (a) Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345–347. (b) Roethle, P. A.; Hernandez, P. T.; Trauner, D. *Org. Lett.* **2006**, *8*, 5901–5904. (c) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *8*, 298–317.

(6) Li, Y.; Pattenden, G. *Nat. Prod. Rep.* **2011**, *28*, 1269–1310.

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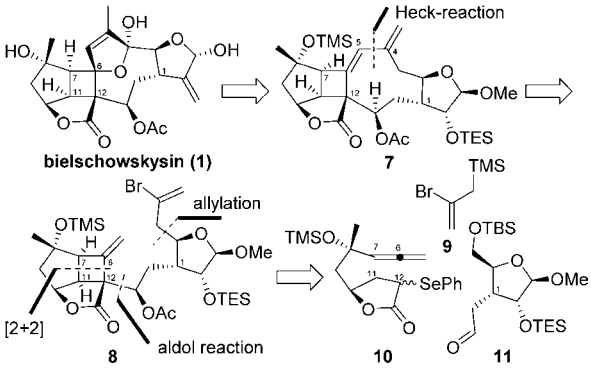
intermediates advanced by Sulikowski (**3**),[3a] Lear (**4**),[3b] Nicolaou (**5**),[4a] and Gosh (**6**)[3c] are deficient in functionalization and **3**–**5** lack the crucial all-carbon quaternary center at C-12 (Scheme 1).

Scheme 2. Retrosynthetic Analysis



Our retrosynthetic plan (Scheme 2) is centered around key intermediate **8**, which was to be assembled from components **9** to **11**. An allylation with 2-bromo-3-trimethylsilyl propene (**9**) should lead to vinyl bromide **8** as the substrate of a palladium mediated Heck macrocyclization. Hopefully, this would furnish cyclononadiene **7** which might be carried on to the final target by allylic oxidation and formation of the dihydrofuran ring.

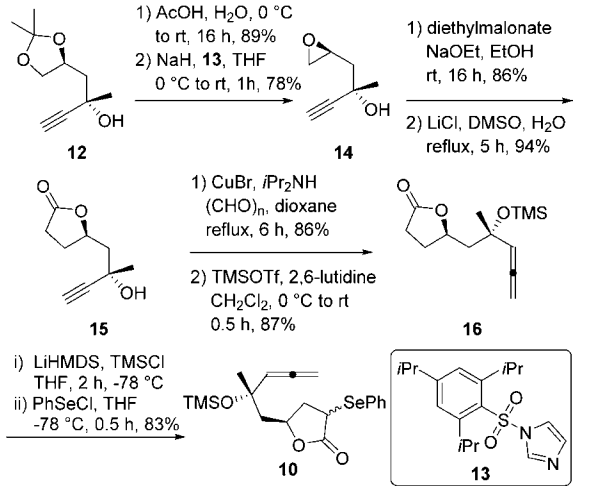
The synthesis of allene **10** (Scheme 3) started with known alkyne **12**, easily available from (−)-malic acid.[3a,b,7] Conversion to epoxide **14** was followed by regioselective ring opening with diethylmalonate. In situ lactonization and Krapcho decarboxylation[8] gave butyrolactone **15** in 56% yield from **12**. The Searles–Crabbé protocol[9] was used for generating the allene. Finally, deprotonation of the lactone, treatment with chlorotrimethylsilane, and addition of phenylselenyl chloride furnished building block **10** as a 1:1.5 mixture of diastereomers in 83% yield.

Coupling partner **11** (Scheme 4) was prepared from known α-D-ribofuranose **17**[10] via lactone **18** (diastereomerically pure). On subjecting the protected diol **19** to Swern oxidation conditions, the primary triethylsilyl protecting group was selectively removed and aldehyde **11** was obtained in 97% yield.

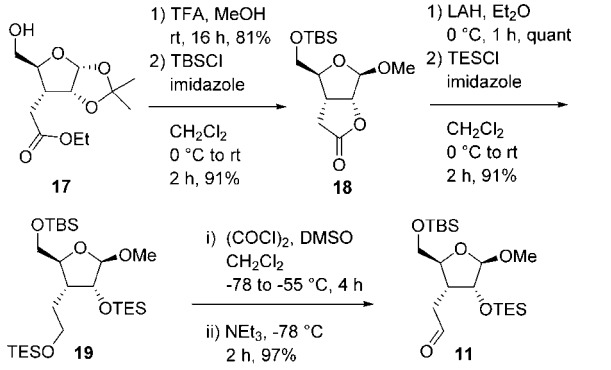
Both building blocks **10** and **11** are readily available in gram quantities and easy to couple by aldol addition. Thus, deprotonation of the seleno lactone **10** at low temperature followed by addition of aldehyde **11** resulted in a mixture of all four diastereomeric adducts which was used without separation in the next step (Scheme 5).

Regioselective oxidative elimination of the phenylselenide gave an inseparable 1:1 mixture of diastereoisomers

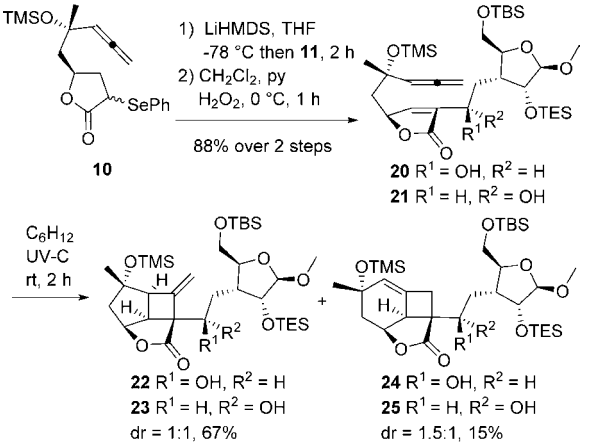
Scheme 3. Preparation of the Allene Building Block



Scheme 4. Preparation of the Coupling Partner



Scheme 5. Fragment Coupling and [2 + 2]-Photocycloaddition



(**20** and **21**) which was irradiated in degassed cyclohexane in quartz tubes with commercially available UV-C-lamps in a homemade UV-reactor for 4 h to provide the tetracyclic photoadducts **22** and **23** in 67% combined yield.

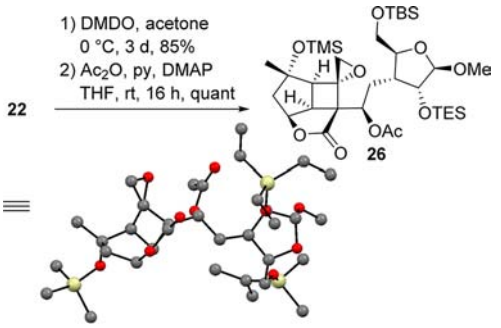
(7) Saito, S.; Hasegawa, T.; Inaba, N.; Nishida, R.; Fujii, T.; Nomizu, S.; Muriwake, T. *Chem. Lett.* **1984**, 1389–1392.

(8) Krapcho, P. A.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138–147.

(9) Searles, S.; Li, Y.; Nassim, B.; Lopes, M.-T. R.; Tran, P. T.; Crabbé, P. *J. Chem. Soc., Perkin Trans. 1* **1984**, 747.

Additionally regioisomers **24** and **25**, originating from the cyclization of the terminal allenic double bond, were isolated in a 15% combined yield. Flash column chromatography at this stage provided us with pure isomers **22** and **23** for the envisaged Heck macrocyclization.

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

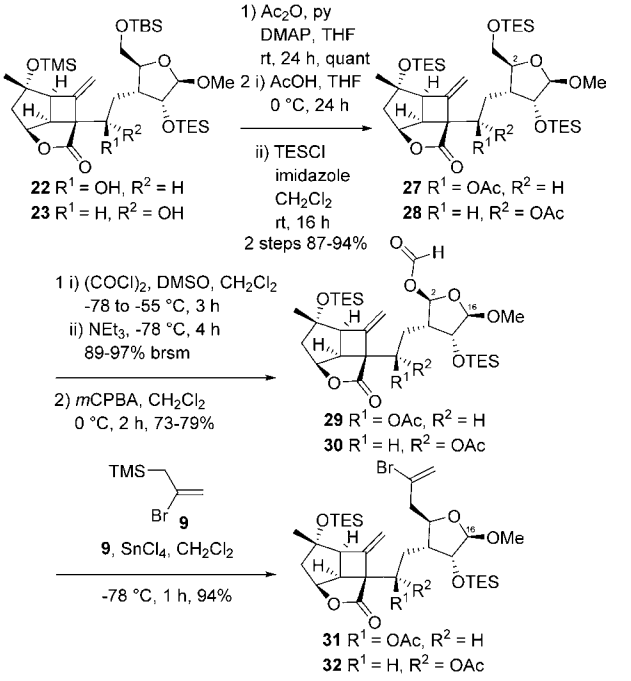


For the assignment of the newly created stereocenters, olefin **22** was epoxidized with a freshly prepared solution of dimethyldioxirane with a d.r. of 6.7:1 (Scheme 6). Standard acetylation provided **26**, suitable for single crystal diffraction.

The synthesis was separately carried on with diastereomerically pure **22** and **23**. To unify the silyl protecting groups, global deprotection with acetic acid in THF was followed by treatment with chlorotriethylsilane to give TES-derivative **27** and **28** in excellent yield (Scheme 7). Again, under the Swern oxidation conditions the primary silyl group was removed selectively. Gratifyingly, Baeyer–Villiger oxidation of the aldehyde with *meta*-chloroperbenzoic acid in dichloromethane at 0 °C was much faster than the epoxidation of the *exo*-methylene group so that formates **29** and **30** were generated in fair yield. Lewis acid mediated allylation with silane **9** gave *trans*-isomers **31** and **32** as single diastereomers, presumably via an oxonium intermediate which was attacked from the less hindered ring face.[11,12] Obviously, the formate is such a superior leaving group that the second anomeric center at C-16 is not touched.

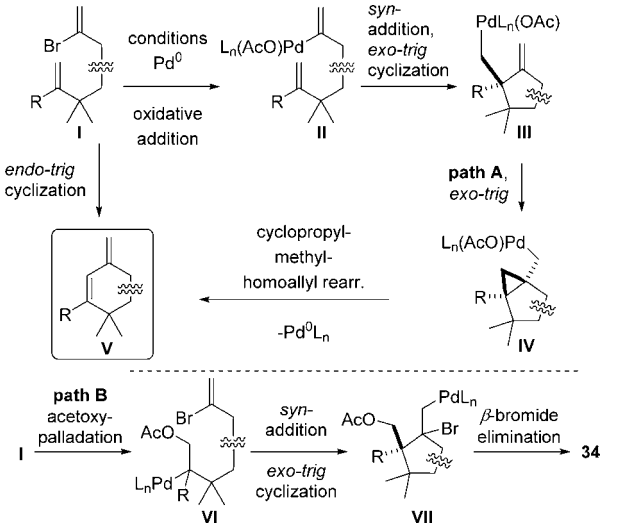
With an appropriate bromoallyl appendage in place we tackled the Heck macrocyclization. Although a preference for *exo*-mode Heck cyclizations exists,[13] *endo*-type reactions have also been observed,[14,15] generally when the

Scheme 7. Introduction of the Bromoallyl Appendage



exo-pathway is precluded. A general mechanistic picture (Scheme 8) suggests that the usual oxidative addition generates σ-alkenylpalladium(II) complex **II** which adds to the *exo*-methylene double bond in a *exo-trig* fashion forming neopentylpalladium intermediate **III**. As β-hydride elimination at this stage is impossible, a 3-*exo-trig* ring closure to cyclopropane **IV** should occur (Scheme 8, path A). Elimination of palladium would then give the desired diene **V** in a formal overall *endo-trig* cyclization.

Scheme 8. Mechanistic Rationalization



A wide variety of Heck conditions were applied to precursors **31** and **32** (Table 1, Supporting Information).

(10) (a) Rosenthal, A.; Nguyen, L. B. *J. Org. Chem.* **1969**, *34*, 1029–1034. (b) Xie, M.; Berges, D. A.; Robins, M. *J. Org. Chem.* **1996**, *61*, 5178–5179 and references cited therein.

(11) (a) Martinez, H. O.; Reinke, H.; Michalik, D.; Vogel, C. *Synthesis* **2009**, *11*, 1834–1840. (b) McDevitt, J.; Lansbury, P. T., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 3818–3828.

(12) Schmitt, A.; Reißig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893–3901.

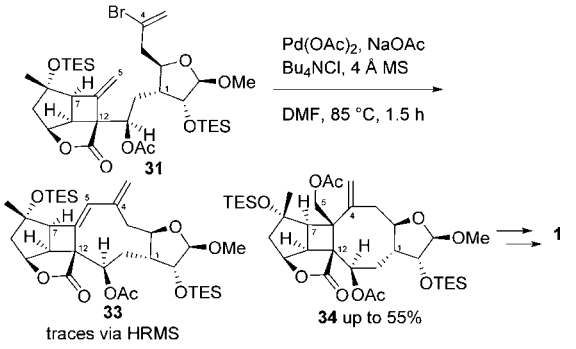
(13) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423–1430. Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. Schulman, J, M.; Friedman, A. A.; Panteleev, J.; Lautens, M. *Chem. Commun.* **2012**, *48*, 55–57.

(14) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379–2411.

(15) Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835 and references cited therein.

For **31**, a standard procedure[16] led to a complex product mixture, in which traces of the desired diene **33** were detected by mass analysis (Scheme 9). Trying to improve this result, we used the findings by Rigby et al.,[15] who have reported that electronic effects and a relatively small metal coordination sphere of the palladium tend to favor the *endo*-pathway in Heck cyclizations. On this basis, we subjected **31** to Jeffery conditions.[17,18] To our surprise, this reaction stereoselectively led to product **34** in 55% yield. Thus, the *exo*-methylene group has been attacked from the less hindered face of the cage-shaped precursor to form a tricyclo[8.3.0.$0^{2,9}$]tridecane ring system instead of the desired "natural" tricyclo[9.3.0.$0^{2,10}$]tetradecane framework (Scheme 9). The stereochemistry and connectivity of **34** were determined by 2D NMR analysis (see Supporting Information).

Scheme 9. Macrocyclization and Carbo-oxygenation



So, obviously unlike the carbohalogenations reported by Lautens[19] and Tong,[20] acetoxy-palladation of **I** to **VI** is followed by *syn*-addition and reductive β-bromide elimination leading to **34** (path B). Thus, an eight-membered macrocycle (**34**) and a newly formed carbon−oxygen bond were generated in a single step from vinyl bromide **31** in acceptable overall yield.

To our knowledge this reaction which converts a 1,1-disubstituted olefin into an allylic neopentyl acetate so far has not been described in the literature.

In conclusion, we have developed a stereocontrolled route to an advanced macrocyclization precursor **31** within a longest linear sequence of 15 steps from the literature known alkyne **12** with an overall yield of 13%. A biomimetic [2 + 2]-photocyclization was used to install the all-carbon quaternary center at C-12. In this step the western [3.2.0]-carbon core of bielschowskysin with all-carbon atoms of the cyclobutane moiety is set up correctly. Moreover, the stereocenters at C-1 and C-2 have been introduced with acetal building block **11**, which could be a suitable building block for other syntheses. The Heck macrocyclization of **31** revealed an unprecedented carbo-oxygenation reaction of a vinyl bromide onto a 1,1-disubstituted double bond. This led to the complex macrocycle **34** featuring a tricyclo[8.3.0.$0^{2,8}$]tridecane ring system and an allylic neopentyl acetate. Work to generalize this methodology is in progress.

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Supporting Information Available. Experimental procedures and full characterization including copies of ^{1}H and ^{13}C NMR spectra and crystal structure analysis of **26** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(16) $Pd(OAc)_2$ (0.1 equiv), PPh_3 (0.2 equiv), Ag_2CO_3 (3.0 equiv), 4 Å MS, toluene (0.01 M), 80 °C, 3 d. For a detailed procedure, see Supporting Information.

(17) (a) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287–1289. (b) Jeffery, T. *Synthesis* **1987**, 70–71. (c) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

(18) $Pd(OAc)_2$ (0.1 equiv), NaOAc (5.0 equiv), Bu_4NCl (2.0 equiv), 4 Å MS, DMF (0.01 M), 85 °C, 1.5 h. For a detailed procedure, see Supporting Information.

(19) (a) Newman, S. G.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 1778–1780. (b) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916–14919.

(20) Liu, H.; Li, C.; Qiu, D.; Tong, X. *J. Am. Chem. Soc.* **2011**, *133*, 6187–6193.

The authors declare no competing financial interest.