The first total synthesis of xenitorins B and C: assignment of absolute configuration†

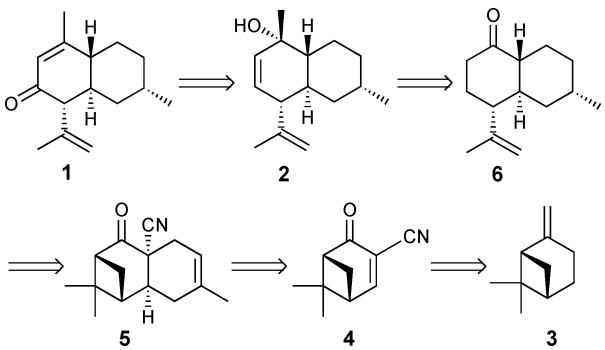
Wen-Sheng Chang,[a] Kak-Shan Shia,[a] Hsing-Jang Liu*[a] and Tai Wei Ly[b]

Received 20th July 2006, Accepted 31st August 2006
First published as an Advance Article on the web 8th September 2006
DOI: 10.1039/b610427d

Starting from (−)-β-pinene, the first total synthesis of xenitorins B and C has been accomplished, which also allowed the assignment of their absolute configuration.

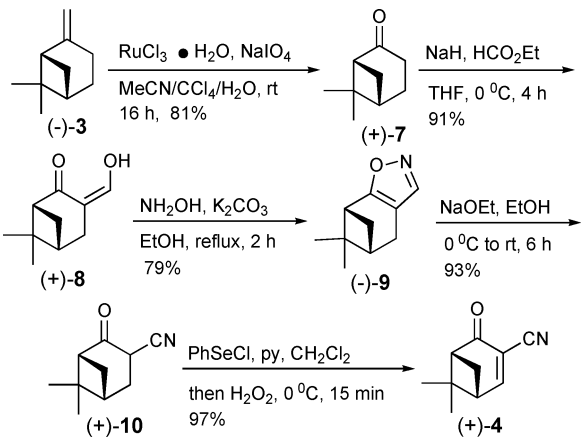
In 2002, Duh *et al.* reported the isolation, from the soft coral *Xenia Puerto-galerae* Roxas collected off the shore of Green Island near Taiwan, of a series of cytotoxic new cadinanoids coined xenitorins, including xenitorins B (**1**) and C (**2**).[1] The structures of these compounds, including relative stereochemistry, were deduced on the basis of extensive spectroscopic studies.[1] Their absolute configuration was, however, unresolved. Herein we wish to report the first total synthesis of xenitorins B (**1**) and C (**2**) in natural form, which serves to confirm the structural assignments, establish the absolute stereochemistry, and provide an easy access to these interesting marine sesquiterpenes.

As depicted in the retrosynthetic scheme (Scheme 1), our synthetic design calls for the use of optically active β-pinene (**3**) both as the starting substrate and source of chirality and its derivative **4** to facilitate the construction of the core system *via* a Diels–Alder reaction (**4** → **5**). This is followed by an acid catalyzed fragmentation process[2] after suitable modifications (**5** → **6**).



Scheme 1

The experimental work† began with the conversion of (−)-β-pinene ((−)-**3**) to (+)-nopinone ((+)-**7**) (Scheme 2). The traditional method to effect this operation involves ozonolysis,[3] a process which is known to be quite hazardous, and several severe explosions were experienced in the past during its application.[4] In light of this, a more secure procedure was employed using ruthenium(III) chloride (0.023 equiv.) and sodium periodate (2.1 equiv.)[5] in aqueous acetonitrile and carbon tetrachloride. (+)-Nopinone ((+)-**7**) thus obtained in 81% yield was subsequently converted to the desired dienophile **4** in the following manner. The introduction of the required cyano group was effected using a well established isoxazole rearrangement protocol.[6,7] Thus, formylation of (+)-**7** followed by treatment of the resulting α-hydroxymethylene ketone (+)-**8**[3,8] with hydroxylamine gave rise to isoxazole (−)-**9**, which was subjected to base-induced rearrangement using sodium ethoxide to afford cyano ketone (+)-**10**, which was found to exist completely in the keto form at room temperature. The dienophilic double bond was subsequently incorporated using the phenylselenenylation-oxidative elimination process[9] to furnish cyano enone (+)-**4** in 65% overall yield from (+)-**7**.

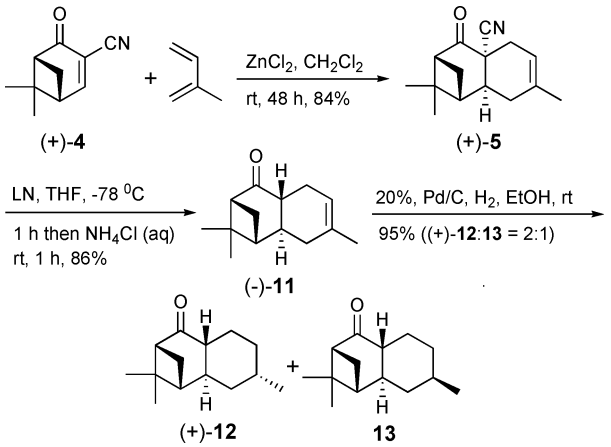


Scheme 2

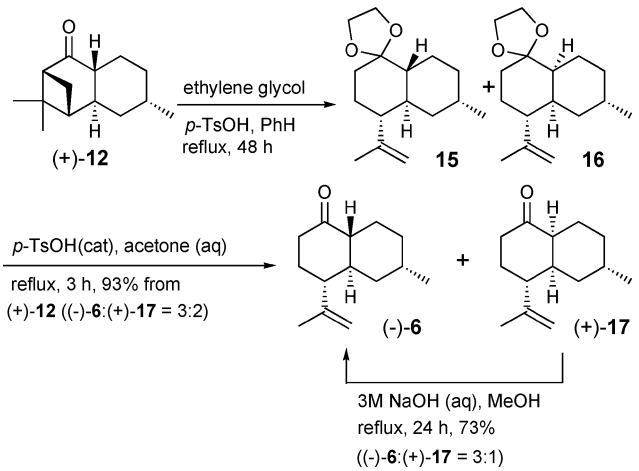
Cyano enone (+)-**4** proved to be an effective dienophile. Its Diels–Alder reaction with isoprene, carried out at room temperature in methylene chloride in the presence of zinc chloride,[10] proceeded with a high degree of efficiency and a completely regio- and stereoselective manner to give adduct (+)-**5** as the sole product in 84% yield (Scheme 3). After serving as an activating group for the Diels–Alder reaction, the angular cyano moiety in (+)-**5** was readily removed by applying a reductive decyanation process developed previously in our laboratories.[11–14] Thus, treatment of (+)-**5** with lithium naphthalenide (LN)[15] in dry tetrahydrofuran followed by protonation gave rise to an 86% yield of enone (−)-**11**[16] as a single product, the stereochemistry of which was suggested by NOE experiments showing no effect

[a]*Department of Chemistry, National Tsing Hua University, Hsinchu, 30013, Taiwan, R. O. C. E-mail: hjliu@mx.nthu.edu.tw; Fax: +886-3-572-0711; Tel: +886-3-573-4292*
[b]*Actimis Pharmaceuticals, Inc. 11099 N. Torrey Pines Rd. Suite 200, La Jolla, CA, 92037, USA. E-mail: twly@actimis.com; Fax: +1-858-678-8576; Tel: +1-858-678-8567*

† Electronic supplementary information (ESI) available: Experimental procedures and spectral characterizations for compounds **1**, **2**, **4**, **5**, **6**, **9**, **10**, **12**, **14**, **17–19** are provided. See DOI: 10.1039/b610427d



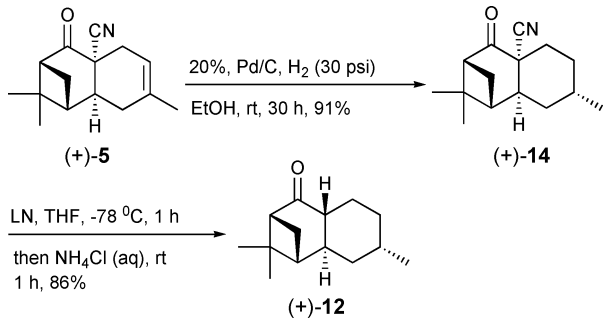
Scheme 3



Scheme 5

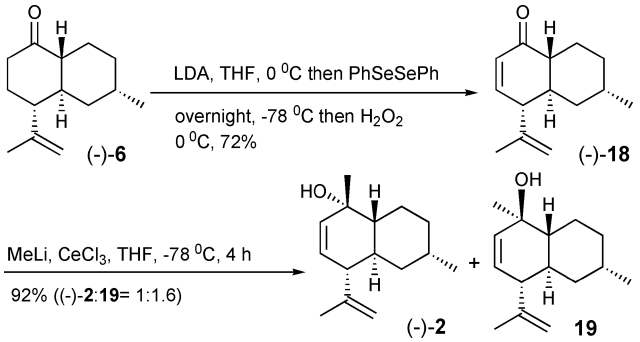
between the fused-ring junction hydrogen atoms. Enone (−)-**11** was subsequently subjected to catalytic hydrogenation using 20% palladium-on-carbon to saturate the olefinic double bond. The reaction proceeded smoothly, but unfortunately produced an intractable mixture of the desired isomer (+)-**12**[17] (*vide infra*) and its epimer **13** in a 2 : 1 ratio.

To circumvent this problem, (+)-**5** was subjected to hydrogenation prior to the removal of the cyano group (Scheme 4), which proved to be highly satisfactory. Catalytic hydrogenation of (+)-**5** in ethanol using 20% Pd/C under 30 psi of hydrogen gave rise to a 91% yield of the desired isomer (+)-**14** as the only product, the configuration of the newly generated stereogenic center was confirmed at a later stage (*vide infra*). Reductive decyanation of (+)-**14** was then performed using LN as the reducing agent, resulting in the formation of ketone (+)-**12** (86% yield). This compound didn't display any NOE effect between the fused-ring junction hydrogen atoms.

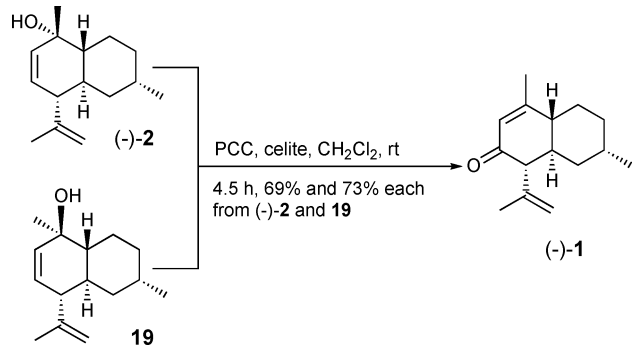


Scheme 4

To complete the core system of the target compounds from (+)-**12**, it remains to selectively cleave the cyclobutane bond linking the quaternary center and the carbon α to the carbonyl. In a previous investigation,[2] it was serendipitously observed that this type of ring cleavage could be effectively achieved under standard ketalization conditions. Accordingly, ketone (+)-**12** was treated with ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene with azeotropic removal of water (Scheme 5). Indeed, the desired fragmentation occurred with concomitant ketalization and partial isomerization to give a mixture of epimeric ketals **15** and **16**, which, upon further treatment with a small amount of *p*-toluenesulfonic acid in refluxing aqueous acetone, gave *trans*-ketone (−)-**6** and its *cis*-isomer (+)-**17** in 3 : 2 ratio and a combined yield of 93% over two steps. These diastereomers were separated, and the relative stereochemistry of the *trans*-isomer (−)-**6** was unambiguously established by X-ray analysis[18,19]‡ while the presumed *cis*-isomer (+)-**17** was treated with sodium hydroxide in refluxing methanol to furnish (−)-**6** as the predominant product. Towards xenitorin C (**2**), ketone (−)-**6** was sequentially treated with lithium diisopropylamide and diphenyl diselenide (Scheme 6).[20] This was immediately followed by oxidative elimination of the ensuing phenylselenenyl intermediate using hydrogen peroxide to give enone (−)-**18** which, on exposure to methyllithium in tetrahydrofuran at 0 °C in the presence of cerium(III) chloride,[21,22] gave rise to xenitorin C ((−)-**2**) in 34% yield along with a 58% yield of its epimer **19**. It was somewhat disappointing that the desired compound (−)-**2** was consistently produced in a lesser amount regardless of the reaction conditions and the reagents applied, as a consequence of the preferential axial addition leading to the undesired stereochemistry. As a small consolation, however, both isomers (−)-**2** and **19** were readily converted to xenitorin B ((−)-**1**) in 69% and 73% yield, respectively, upon treatment with pyridinium chlorochromate on Celite[23] in methylene chloride (Scheme 7). The identity of the synthetic compounds and the corresponding natural products was established by direct comparison of their ^{1}H nmr spectra.[1] As well, other spectral data and physical properties, including specific rotations of the synthetic



Scheme 6



Scheme 7

materials, were also shown to be in excellent agreement with those reported for the naturally occurring compounds.[1] Thus, the first total synthesis of xenitorins B ((−)-**1**) and C ((−)-**2**) has been achieved and serves to unambiguously establish the absolute configuration of these structurally interesting natural products.

Acknowledgements

We are grateful to the National Science Council of the Republic of China for financial support and to Professor C. Y. Duh of National Sun Yat-Sen University for ^{1}H nmr spectra of the natural xenitorins B and C.

Notes and references

‡ CCDC reference numbers 602444. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b610427d

1 C. Y. Duh, S. C. Chien, P. Y. Song and S. K. Wang, *J. Nat. Prod.*, 2002, **65**, 1853.
2 H. J. Liu, S. Y. Chew, E. N. C. Browne and J. B. Kim, *Can. J. Chem.*, 1994, **72**, 1193.
3 H. J. Liu, Y. Li and E. N. C. Browne, *Can. J. Chem.*, 1994, **72**, 1883.
4 (*a*) P. M. Gordon, *Chem. Eng. News*, 1990, **68**(32), 2; (*b*) J. T. B. Ferreira, *Chem. Eng. News*, 1990, **68**(50), 4.
5 C. L. Queiroga, V. L. Ferracini and A. J. Marsaioli, *Phytochemistry*, 1996, **42**, 1097 and references therein.
6 M. Kim, R. S. Gross, H. Sevestre, N. K. Dunlap and D. S. Watt, *J. Org. Chem.*, 1988, **53**, 93.
7 S. Takagi and H. Yasuda, *Yakugaku Zasshi*, 1959, **79**, 467.
8 For alternative formylation procedures of compound **7** to give compound **8**, see: (*a*) A. V. Malkov, M. Bella, I. G. Stará and P. Kočovský, *Tetrahedron Lett.*, 2001, **42**, 3045; (*b*) B. Kolp, D. Abeln, H. Stoeckli-Evens and A. von Zelewsky, *Eur. J. Inorg. Chem.*, 2001, 1207; (*c*) G. Chelucci, G. Loriga, G. Murineddu and G. A. Pinna, *Synthesis*, 2003, 73.
9 D. Liotta, R. P. Barnum, G. Zima, C. Bayer and H. S. Kezar, III, *J. Org. Chem.*, 1981, **46**, 2920.
10 (*a*) J. L. Zhu, K. S. Shia and H. J. Liu, *Chem. Commun.*, 2000, 1599; (*b*) H. J. Liu and J. Yip, *Synlett*, 2000, 1119.
11 K. S. Shia, N. Y. Chang, J. Yip and H. J. Liu, *Tetrahedron Lett.*, 1997, **38**, 7713.
12 H. J. Liu, J. L. Zhu and K. S. Shia, *Tetrahedron Lett.*, 1998, **39**, 4183.
13 C. L. Tai, T. W. Ly, J. D. Wu, K. S. Shia and H. J. Liu, *Synlett*, 2001, 214.
14 T. Y. Tsai, K. S. Shia and H. J. Liu, *Synlett*, 2003, 97.
15 For the preparation of a stock solution of LN in THF, see: (*a*) H. J. Liu, J. Yip and K. S. Shia, *Tetrahedron Lett.*, 1997, **38**, 2253; (*b*) H. J. Liu and X. Shang, *Tetrahedron Lett.*, 1998, **39**, 367.
16 For alternative approaches to compound **11** see: (*a*) L. Minuti, R. Selvaggi, A. Taticchi, E. Gacs-Baitz and D. Matchytka, *Synth. Commun.*, 1991, **21**, 2143; (*b*) H. J. Liu, S. Y. Chew and E. N. C. Browne, *Tetrahedron Lett.*, 1991, **32**, 2005 and ref. 2.
17 Compound **12** has been previously reported by this research group (see ref. 16*b*).
18 Crystal structure data for (−)-**6** has been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 602444. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.
19 Chemical formula ($C_{14}H_{22}O$), formula weight (206.32), crystal system (monoclinic), unit cell dimensions ($a = 9.1809(18)$ Å, $b = 6.4336(12)$ Å, $c = 11.416(2)$ Å, $\alpha = \gamma = 90°$, $\beta = 108.320(4)°$), unit cell volume (640.1(2) Å^3), $Z = 2$, temperature (294(2) K), space group ($P2(1)$), absorption coefficient (0.065 mm^{-1}), reflections collected (4800), independent reflections including Friedel pairs (3005), $R_{int} = 0.0500$, $R1 = 0.0441$, $wR2 = 0.0974$ for observeddata, $I > 2\sigma(I)$. No conclusion pertaining to the absolute stereochemistry of (−)-**6** is drawn from this X-ray analysis.
20 H. J. Reich, J. M. Renga and I. L. Reich, *J. Am. Chem. Soc.*, 1975, **97**, 5434.
21 T. Imamoto, *Lanthanides in Organic Synthesis*, Academic Press, New York, 1994, Section 5.4.
22 H. J. Liu, K. S. Shia, X. Shang and B. Y. Zhu, *Tetrahedron*, 1999, **55**, 3803.
23 H. C. Brown, C. O. Grag and K. T. Liu, *J. Org. Chem.*, 1971, **36**, 387.