ORGANIC
LETTERS

2009
Vol. 11, No. 21
4842−4845

A Novel *Cis*-Selective Cyclohexanone Annulation as the Key Step of a Total Synthesis of the Sesquiterpene Isoacanthodoral

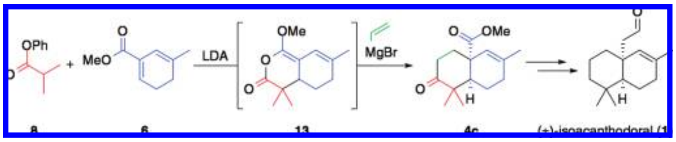
Thomas Hampel and Reinhard Brückner*

Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, 79104 Freiburg im Breisgau, Germany

reinhard.brueckner@organik.chemie.uni-freiburg.de

Received August 14, 2009

ABSTRACT



Isoacanthodoral (1) is a structurally unique sesquiterpene in that it is a bicyclo[4.4.0]dec-1-ene with a *cis*- rather than the common *trans*-junction between the constituting rings. An efficient construction of this motif has been accomplished by a novel *cis*-selective cyclohexanone annulation, combining the lithium enolate of ester 8, the α,*β*-unsaturated ester 6, and vinylmagnesium bromide in a single synthetic operation. For completing the total synthesis of 1, a Shapiro-olefination/hydrogenation sequence and a reductive cyanation were employed.

Nudibranches are marine mollusks devoid of a protective shell. Many of them seem to make up for the resulting vulnerability by excreting strong odorants—lethal both to fish and crustaceans.[1] For humans, the scent of nudibranches is fruity as long as perceived in minute concentrations but so malodorous at higher concentrations that it causes nausea.

Isoacanthodoral (**1**) is an odorous sesquiterpene from this class of compounds (Figure 1). Along with other terpenoids, it was isolated from the nudibranch *Acanthodoris nanaimoensis*, which thrives on the Canadian Pacific coast.[2] The compound is structurally unique in that it constitutes a bicyclo[4.4.0]dec-1-ene displaying a *cis*- rather than the common *trans*-junction between the constituting rings. While investigating the total synthesis of a tricyclic terpenoid, which contains both a *cis*- and a *trans*-fused bicyclo[4.4.0]decane moiety we became interested in accessing such motifs and their unsaturated analogues—like terpenoid **1**—efficiently.

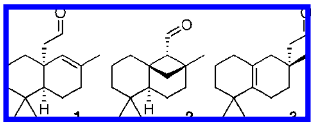


Figure 1. Sesquiterpenes isoacanthodoral (**1**), acanthodoral (**2**), and nanaimoal (**3**) isolated from *A. nanaimoensis*.

To date, **1** has been synthesized once, as a racemic mixture and with an expenditure of 16 steps in the longest linear sequence.[3] The approach featured an intermolecular Diels−Alder reaction between 2-(methoxycarbonyl)-4,4-dimethylcyclohexa-2,5-dien-1-one and isoprene as the key step; the dienophile was derived from 4,4-dimethylcyclohex-2-en-1-one.[3a]

In our retrosynthetic analysis, the aldehyde-containing *cis*-bicyclo[4.4.0]decene **1** was traced back to the chain-

---

[1] Andersen, R. Skin chemistry of nudibranchs from the West Coast of North America. In *Molluscs*; Cimino, G., Ed.; Springer: Berlin, 2006; pp 277−301.

[2] Ayer, S. W.; Andersen, R. J.; He, C. H.; Clardy, J. *J. Org. Chem.* **1984**, *49*, 2653–2654.

[3] (a) Liu, H.-J.; Browne, E. N. C. *Can. J. Chem.* **1981**, *59*, 601–608. (b) Liu, H.-J.; Ulíbarri, G.; Nelson, L. A. K. *J. Chem. Soc., Chem. Commun.* **1990**, 1419–1421. (c) Liu, H.-J.; Ulíbarri, G.; Nelson, L. A. K. *Can. J. Chem.* **1994**, *72*, 2416–2427.

10.1021/ol9018979 CCC: $40.75

shortened ester-containing *cis*-bicyclo[4.4.0]decenone **4c** (Figure 2). An obvious disconnection of **4c** would be into silyldienol ether **7c** and dienophile **6**. This would allow for a *cis*-selective cyclohexanone annulation either by an anionic Diels−Alder reaction of the corresponding lithium dienolate **5c** or by an equivalent sequence of two Michael additions. Alternatively, we envisioned that the *cis*-bicyclo[4.4.0]decenone **4c** results from three components and two Michael additions, i.e., from a novel domino process.[4] In its course, the enolate of ester **8**, the previously mentioned α,*β*-unsaturated ester **6**, and vinylmagnesium bromide (**9**) would combine in a series of steps, which could probably be performed as a one-pot operation.

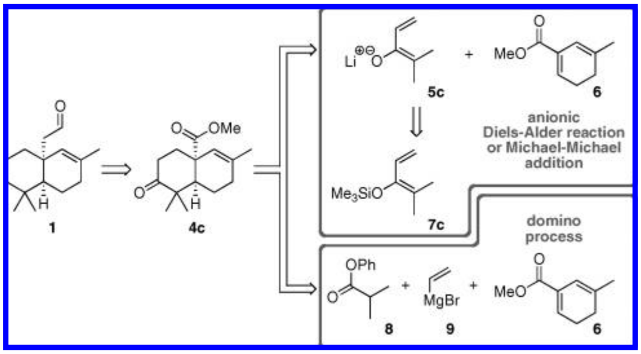
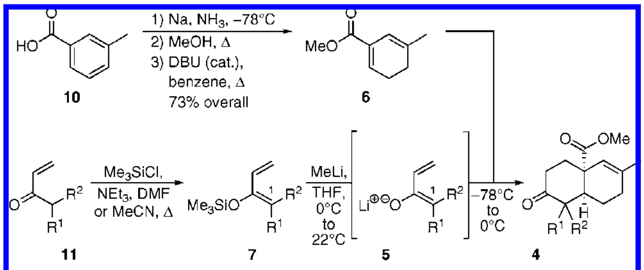


Figure 2. Two retrosynthetic analyses of isoacanthodoral (**1**).

Anionic Diels−Alder reactions, i.e., [4 + 2]-additions of oxyanion-substituted dienes (“dienolates”) to dienophiles do not represent widely used approaches to cyclohexanones.[5] Their best known variants employ cyclohexenones[6] or alk-3-en-2-ones with an electron-withdrawing 1-substituent (“Nazarov reagents”[7])[8] as dienolate precursors, combined with a base (LDA[6] and cesium carbonate,[8] respectively).

Other than the mentioned enones, enone **11c** and its less hindered analogues **11a** and **b** (Scheme 1, bottom) self-condensed during attempted dienolate generation by deprotonation. This problem was avoided when we transformed these compounds into silyldienol ethers **7a**−**c** (11−27% yield, not optimized[9]) and treated the latter with methyllithium for releasing the corresponding dienolates. Dienophile **6** was prepared from *m*-toluic acid (**10**) in three steps[10] and 73% overall yield (Scheme 1, top).

Scheme 1. Anionic Diels−Alder Reaction (or Michael−Michael Addition)



11	R^1	R^2	**7**	yield	**5**	**4**	yield
a	H	H	**a**	27%	**a**	**a**	67%
b	Me	H	**b**	27%[a]	**b**	**b**	39-53%[b]
c	Me	Me	**c**	11%	**c**	**c**	18%

[a] *E*:*Z* = 15:85. [b] *ds* = 66:34 (not assigned).

The anionic Diels−Alder reaction (or synthetically equivalent sequence of two Michael additions) worked best for the dienolate (**5a**) with the fewest 1-substituents: following this pathway, silyldienol ether **7a** rendered *cis*-bicyclo[4.4.0]decenone **4a** in 67% yield. Annulation yields were limited to 39−53% and 18%, however, when the sterically more hindered silyldienol ethers **7b** or **7c** were employed. Faced with the latter result and aggravating purification and yield problems during the preparation of enone **11c** (cf. Supporting Information), we abandoned this route toward **1** as unexpedient.

A better working approach to the bicyclo[4.4.0]decenone **4c** was established by the *cis*-selective cyclohexanone annulation shown in Scheme 2. It is a five-step, one-pot process, novel (to the best of our knowledge), and entails the following course of events: A Michael addition (1) of the **8**-derived lithium enolate to the cyclohexadienoate **6** delivers the methyl ester enolate **12**. The latter undergoes *O*-acylation intramolecularly (2) so that the ketene acylal **13** is formed. The addition of vinylmagnesium bromide (3) generates hemiacylal **14**, which ring-opens (4) upon warming and delivers the enone-substituted ester enolate **15**, which in turn ring-closes by an intramolecular Michael addition (5).

---

(4) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. Domino Reactions in Organic Synthesis; Wiley-VCH: Weinheim, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Angew. Chem. **2006**, *118*, 7292–7344. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (c) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551–564.

(5) Reviews about Diels−Alder reactions: (a) Marsault, E.; Toro, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243–4260. (b) Corey, E. J. *Angew. Chem.* **2002**, *114*, 1724–1741. Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1650–1667. (c) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem.* **2002**, *114*, 1742–1773. Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 1668–1698. (d) Takao, K.; Munakata, R.; Tadano, K. *Chem. Rev.* **2005**, *105*, 4779–4807. (e) Ess, D. H.; Jones, G. O.; Houk, K. N. *Adv. Synth. Catal.* **2006**, *348*, 2337–2361. (f) Wessig, P.; Mueller, G. *Chem. Rev.* **2008**, *108*, 2051–2063. (g) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359–5406.

(6) First report: (a) Lee, R. A. *Tetrahedron Lett.* **1973**, 3333–3336. Representative applications: (b) Spitzner, D.; Engler, A. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. 8, pp 219−222, and references cited therein.

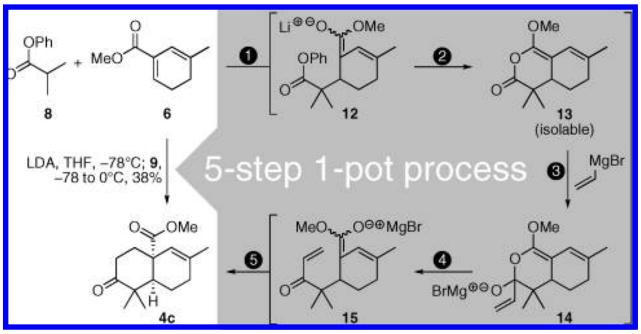
(7) Nazarov, I. N.; Zavyalov, S. I. *Zh. Obshch. Khim.* **1953**, *23*, 1703–1705. Nazarov, I. N.; Zavyalov, S. I. *Russ. J. Org. Chem.* **1953**, *23*, 1793–1794. Nazarov, I. N.; Zavyalov, S. I. *Chem. Abstr.* **1954**, *48*, 13667h.

(8) First report: (a) Lavallée, J.-F.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 5117–5118. (b) Lead reference for subsequent studies: Chen, L.; Deslongchamps, P. *Can. J. Chem.* **2005**, *83*, 728–740. Erratum: Chen, L.; Deslongchamps, P. *Can. J. Chem.* **2005**, *83*, 2144.

(9) The considerable volatility of silyldienolethers **7a**−**c** and their sensitivity toward hydrolysis may account in part for the low yields preparing them.

(10) Kaliappan, K.; Subba Rao, G. S. R. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3387–3392.

Scheme 2. Cyclohexanone Annulation by a Domino Process



All in all, the *cis*-bicyclo[4.4.0]decenone **4c** resulted as a single diastereomer in 38% yield as unambiguously proven by the crystal structure analysis featured as Figure 3.

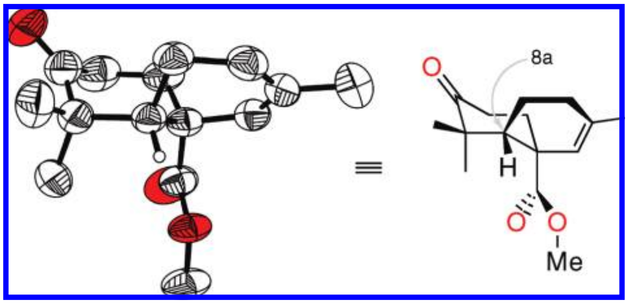


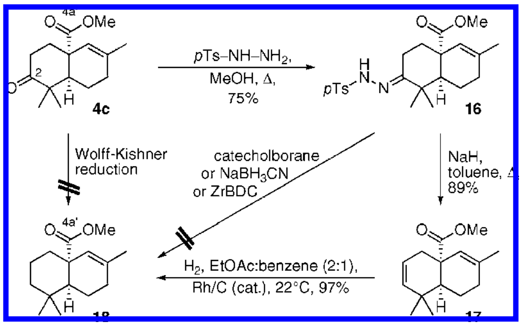
Figure 3. ORTEP plot of bicyclo[4.4.0]decenone **4c** (ellipsoids: 50% probability; all H atoms other than 8a-H were omitted for clarity).[11]

The phenyl ester of thioisobutyric acid was less suited for providing ketene acylal **13** and the annulation product **4c** than the sulfur-free analogue **8**. The lithium enolates of methyl or *tert*-butyl isobutyrate underwent Michael additions to **6**, i.e., step 1 of Scheme 2 without step 2 ensuing. Employing vinyllithium rather than vinylmagnesium bromide in step 3 lowered the yield by more than 50%.

In support of the proposed mechanism we were able to isolate the ketene acylal intermediate **13** after workup at 0 °C.[12,13] The purified specimen of **13** continued to react according to the domino process of Scheme 2 when it was treated with vinylmagnesium bromide at −78 °C, and the reaction mixture gradually warmed to room temperature. This *modus procedendi* rendered *cis*-bicyclo[4.4.0]decenone **4c** in 39% yield.

To complete the total synthesis of (±)-isoacanthodoral (**1**), bicyclo[4.4.0]decenone **4c** had to be defunctionalized at C-2 (cf. Scheme 3) and C$_1$-elongated at C-4a′ (cf. Scheme 4).

Scheme 3. Defunctionalization of Ketone **4c** at C-2[a]



[a] ZrBDC = $Zr(BH_4)_2Cl_2(dabco)_2$.[14]

All attempts to defunctionalize bicyclo[4.4.0]decenone **4c** at C-2 by a Wolff−Kishner reduction, i.e., in a single operation, failed no matter whether under the Huang-Minlon ($N_2H_4\cdot H_2O$, KOH, 120 °C; 200 °C)[15] or Cram ($N_2H_4\cdot H_2O$, KO*t*Bu, 70 °C)[16] conditions. As the prelude to another one-step reduction bicyclo[4.4.0]decenone **4c** was converted into the tosylhydrazone **16** (75% yield). Yet contrary to our expectations, **16** could not be turned into the half-saturated ester **18** by a variety of reducing agents: catecholborane,[17] $NaBH_3CN$,[18] or $Zr(BH_4)_2Cl_2(dabco)_2$.[14] Gratifyingly, a Shapiro olefination[19] of tosylhydrazone **16** rendered dienoic ester **17**, which could be hydrogenated completely regioselectively at the less substituted C=C double bond using 5% Rh on charcoal as a catalyst. Therefore, the monounsaturated ester **18** resulted in 86% yield over the two steps.

Our initial plan called for transforming the carboxylic center C-4a′ of ester **18** into the $CH_2{-}CH{=}O$ moiety of the target structure (**1**) either by the attack of an appropriate C$_1$-nucleophile upon the corresponding alkylating agent **22** or by advancing to the epoxide **23** and subjecting the latter to a semipinacol rearrangement (Scheme 4). En route to both options, ester **18** was reduced with DIBAL to give the “neopentylic” alcohol **19**. Attempted transformations of **19** into alkylating agents **22** failed for a variety of leaving groups

---

(11) CCDC 743905 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via the link www.ccdc.cam.ac.uk/data_request/cif.

(12) Regarding the oxidation states of the dioxygenated carbon atoms, ketene acylal **13** can be viewed as a monoenol ether of a carboxylic anhydride. This structural motif can be found in more than 800 compounds, most of them aromatic. For selected nonaromatic examples (like **13**), see ref 13.

(13) (a) Reid, E. B. *J. Am. Chem. Soc.* **1950**, *72*, 2853–2855. (b) White, E. H.; Steinmetz, M. G.; Miano, J. D.; Wildes, P. D.; Morland, R. *J. Am. Chem. Soc.* **1980**, *102*, 3199–3208. (c) Mezger, F.; Simchen, G.; Fischer, P. *Synthesis* **1991**, 375–378.

(14) Alinezhad, H.; Tajbakhsh, M.; Salehian, F. *Synlett* **2005**, 170–172.

(15) Method : Tenius, B. S. M.; Schroeder, E. K. *Synth. Commun.* **2000**, *30*, 1371–1378.

(16) Method: Secci, F.; Frongia, A.; Ollivier, J.; Piras, P. P. *Synthesis* **2007**, 999–1002.

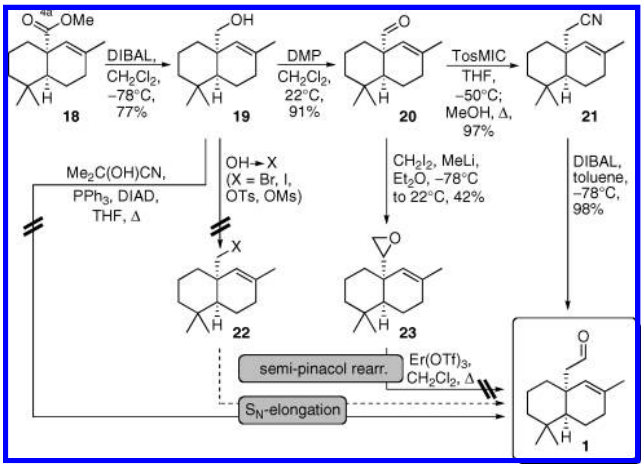
(17) Method: Chapdelaine, M. J.; Warwick, P. J.; Shaw, A. *J. Org. Chem.* **1989**, *54*, 1218–1221.

(18) Method : Freitas, J. M.; Abrantes, L. M.; Darbre, T. *Helv. Chim. Acta* **2005**, *88*, 2470–2478.

(19) Reviews about Shapiro olefinations: (a) Shapiro, R. H. *Org. React.* **1976**, *23*, 405–507. (b) Adlington, R. M.; Barrett, A. G. M. *Acc. Chem. Res.* **1983**, *16*, 55–59. (c) Chamberlin, A. R.; Bloom, S. H. *Org. React.* **1990**, *39*, 1–83.

(X = Br, I, OTs, and OMs) or led to a Wagner−Meerwein rearrangement product. In situ activation of alcohol **19** under the conditions of a Mukaiyama redox condensation in the presence of acetone cyanohydrin as a cyanide source[20] was similarly unsuccessful.

Scheme 4. C_1-Elongation of Ester **18** at C-4′ and Completion of the Synthesis[a]



[a] TosMIC = tosylmethyl isocyanide.[21]

Coming closer to success, oxidation of alcohol **19** with the Dess−Martin periodinane[22] furnished aldehyde **20** in 91% yield (Scheme 4). When **20** was treated with methyllithium in the presence of diiodomethane,[23] the desired epoxide **23** became accessible in 42% yield as a 60:40 mixture with ketone **24**. The latter must have arisen from an over-reaction of **23** through a semipinacol rearrangement (not optimized, vide infra).[24] At odds with the formation of **24** from this *undesired* semipinacol rearrangement, a *deliberately* induced semipinacol rearrangement of the **23**/**24** mixture by an established procedure, i.e., exposure to 1 mol % of $Er(OTf)_3$,[25] did not convert its fraction of epoxide **23** into the desired (target!) aldehyde as expected,[25] but delivered another rearrangement product.

After extensive experimentation, it was found that aldehyde **20** could be homologized in 95% yield to give the title compound (**1**):[26] by an initial reductive cyanation with tosylmethyl isocyanide[21] and a subsequent reduction of nitrile **21** (Scheme 4). This procedure allowed a remarkably facile C_1-elongation in a neopentylic position in a remarkably good yield.

In summary, we have developed a novel *cis*-selective cyclohexanone annulation—combining the enolate of ester **8**, the α,β-unsaturated ester **6**, and vinylmagnesium bromide in a domino reaction—and applied it to a total synthesis of (±)-isoacanthodoral (**1**). Eleven steps in the longest linear sequence and 12% overall yield make our approach significantly shorter than its predecessor. Studies toward an application of our cyclohexanone annulation in the total synthesis of tricyclic terpenoids as well as toward an asymmetric annulation variant are underway in our laboratory.

Acknowledgment. We thank Dr. J. Geier (Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg) for solving the X-ray structure of **4c**, Dr. M. Keller (Institut für Organische Chemie und Biochemie, Albert-Ludwigs-Universität Freiburg) for NMR experiments, and BASF SE for generous gifts of chemicals.

Note Added after ASAP Publication. There were errors in the TOC/abstract graphic in the version published ASAP September 23, 2009; the correct version published ASAP September 24, 2009.

Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9018979

---

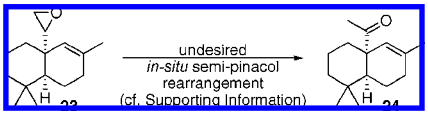
(20) Method: Ghosh, A. K.; Moon, D. K. *Org. Lett.* **2007**, *9*, 2425–2427.

(21) Modification of the method developed by: van Leusen, A. M.; Oomkes, P. G. *Synth. Commun.* **1980**, *10*, 399–403.

(22) Method: Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.

(23) Method: Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-C. *J. Org. Chem.* **2008**, *73*, 6258–6264.

(24)



(25) Procopio, A.; Dalpozzo, R.; De Nino, A.; Nardi, M.; Sindona, G.; Tagarelli, A. *Synlett* **2004**, 2633–2635.

(26) All spectroscopic and analytical data of **1** were identical to those reported previously.[3c]