J|A|C|S
COMMUNICATIONS

Published on Web 07/18/2002

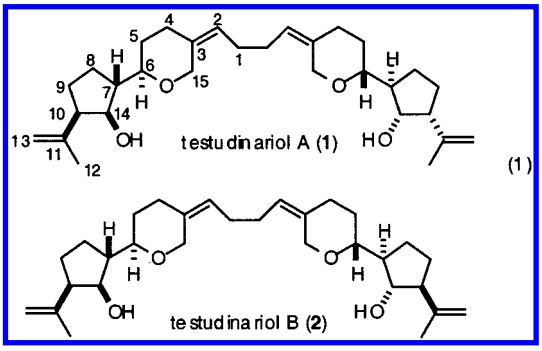
Enantioselective Total Synthesis of (+)-Testudinariol A Using a New Nickel-Catalyzed Allenyl Aldehyde Cyclization

Kande K. D. Amarasinghe and John Montgomery*

Department of Chemistry, Wayne State University, Detroit, Michigan 48202

Received June 3, 2002

Testudinariols A and B are epimeric triterpene marine natural products that were originally isolated from the skin and the mucus of the marine mollusc *Pleurobranchus testudinarius* by Spinella (eq 1).[1] Testudinariol A (**1**) possesses C_2 symmetry, whereas



(1)

testudinariol B (**2**) lacks symmetry. The structures possess a highly functionalized cyclopentanol framework with four contiguous stereocenters appended to a central 3-alkylidene tetrahydropyran. Total syntheses of testudinariols A and B were recently accomplished by Mori,[2] and a formal synthesis of testudinariol A was published by Kodama.[3] Given the difficulties in efficiently controlling the stereochemical issues presented by these structurally intriguing natural products, we have developed a novel strategy for the preparation of testudinariol A. In the context of this effort, we have developed a new nickel-catalyzed reaction for the cyclization of allenyl aldehydes, and we have utilized complex applications of the Abiko−Masamune asymmetric aldol reaction[4] and the Overman oxocarbenium ion/vinyl silane condensation process.[5] The combination of these procedures has provided an efficient total synthesis of (+)-testudinariol A.

We chose to investigate an asymmetric anti aldol reaction to control the critical acyclic C-6/C-7 relative and absolute stereochemistry.[4] Functionalization of allenyl acid chloride **3** with the norephedrine-derived chiral auxiliary **4** provided ester **5** in 99% yield (Scheme 1). According to the conditions reported by Abiko and Masamune, enolization of **5** with $(c\text{-hex})_2$BOTf and triethylamine in dichloromethane followed by treatment with 3-benzyloxypropionaldehyde afforded aldol adduct **6** as a 97:3 ratio of anti:syn diastereomers in 72% yield. Diastereoselectivity within the anti manifold was 90:10. Interestingly, the original reports from Abiko and Masamune were restricted to the preparation of propionate aldols, but the synthesis of the more functionalized substrate **5** similarly proceeded cleanly with very good control of stereochemistry. Protection of **6** as the methoxyethoxymethyl (MEM) ether followed by conversion of the ester linkage to an aldehyde by $LiAlH_4$ reduction and Swern oxidation afforded aldehyde **7** in 64% yield over three steps.

With substrate **7** in hand, we considered the development of a new cyclization process to prepare the requisite functionalized cyclopentanol core. In analogy to nickel-catalyzed ynal cyclizations previously developed in our laboratory,[6] we anticipated that the analogous nickel-catalyzed cyclization of an allenyl aldehyde with dimethylzinc would afford the desired core structure. After some optimization, the desired cyclization was developed with exceptionally high stereocontrol. Accordingly, substrate **7** was treated with dimethylzinc, Ti(O-*i*-Pr)$_4$, and 10 mol % Ni(COD)$_2$ in THF to afford cyclopentanol **10** in 62% yield in >97:3 diastereoselectivity. Ti(O-*i*-Pr)$_4$ is not a required additive in this reaction, although its use leads to higher yields and diastereoselectivities. We propose that the mechanism of this novel process involves formation of a Ni(0) π-complex **8** with the aldehyde and proximal allene π-systems coordinating to nickel in an eclipsed fashion with a pseudoequatorial orientation of the side chain (Scheme 2). Oxidative cyclization to metallacycle **9**, followed by dimethylzinc transmetalation and reductive elimination, would afford the observed stereochemistry of product **10**.[7,8] This combination of an asymmetric anti aldol reaction to control the acyclic stereochemistry and a nickel-catalyzed cyclization to control the cyclic stereochemistry provides a powerful combination for the construction of ring systems such as **10**.

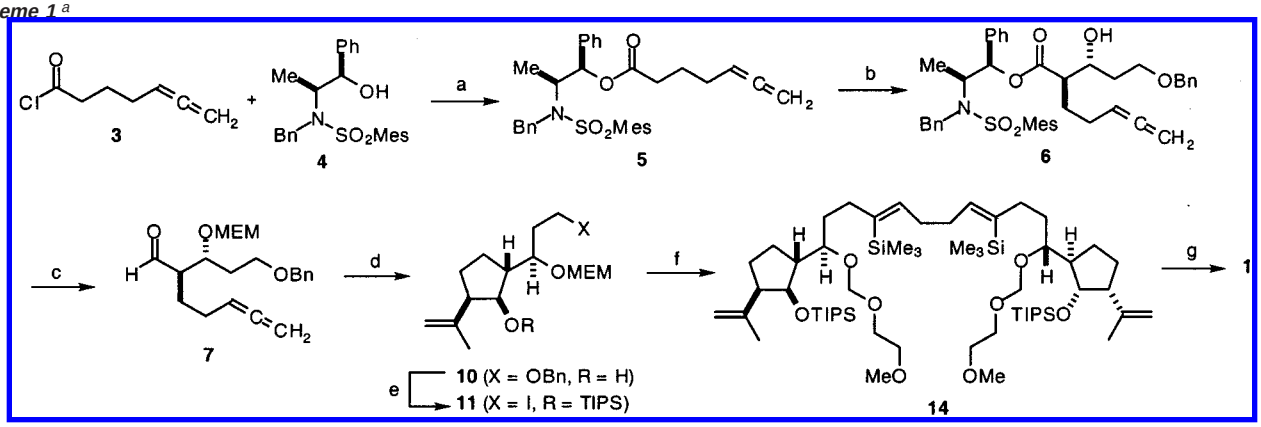
Protection of alcohol **10** as the TIPS ether, followed by Li^0/NH_3 debenzylation and conversion of the resulting primary hydroxyl to the iodide with PPh_3/I_2 and imidazole, allowed the formation of **11** in 75% yield over three steps. Assembly of the C_2-symmetrical core structure then required preparation of bis(vinyl bromide) **13** (Scheme 3). Bromination of 1,5-hexadiene, followed by elimination with LDA and silylation, afforded bis(silyl acetylene) **12**.[9] DIBAL reduction and bromination resulted in the formation of bis(vinyl bromide) **13**.[10] Metal−halogen exchange with *s*-BuLi in THF afforded a dianion which was alkylated with primary iodide **11**.[11] By employing a 3:1 stoichiometry of iodide **11** to the dianion of **13**, a 38% yield of bis(vinyl silane) **14** was obtained along with 13% of monoalkylated material and a 54% recovery of **11**.

To complete the synthesis, a two-directional oxocarbenium ion/vinyl silane cyclization was carried out.[5] A 0.1 M, −78 °C dichloromethane solution of bis(vinyl silane) **14** was treated with 10 equiv of Et_2AlCl, and the mixture was allowed to warm to room temperature. Upon cooling of the mixture back to −78 °C and quenching with 2 M NaOH, clean conversion to the bis-tetrahydropyran was observed. To our knowledge, this represents the first two-directional oxocarbenium ion cyclization of this type.[12] The crude material was then treated with *n*-Bu_4NF to afford (+)-testudinariol A (**1**) in 55% yield over two steps. NMR spectral data were identical to those previously reported {$[\alpha]^{25}_D$ =

* Address correspondence to this author. E-mail: jwm@chem.wayne.edu.

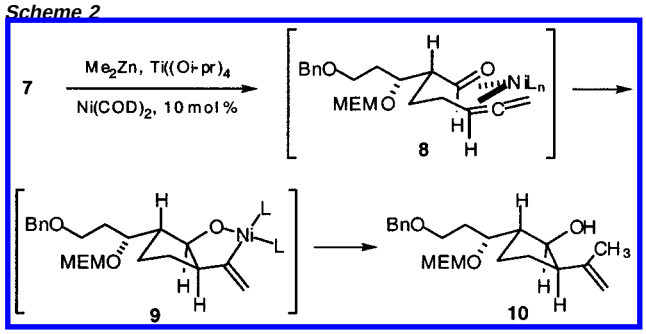
10.1021/ja027148y CCC: $22.00

Scheme 1 [a]

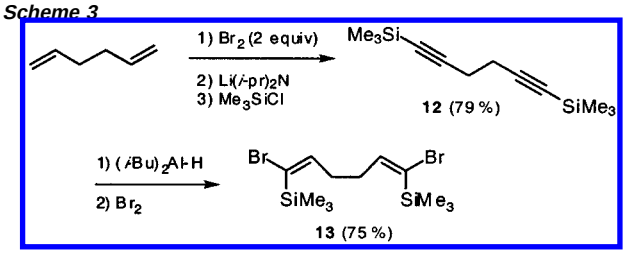


[a] (a) Pyridine, CH_2Cl_2, 0 °C to room temperature, 99%. (b) (*c*-hex)$_2$BOTf, Et_3N, CH_2Cl_2, −78 °C, then HC(O)CH_2CH_2OBn, −78 to 0 °C, 72%. (c) i. $CH_3OCH_2CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature, 79%; ii. $LiAlH_4$, THF, 0 °C, 87%; iii. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 93%. (d) Ni(COD)$_2$ (10 mol %), Me_2Zn, Ti(O-*i*-Pr)$_4$, THF, 0 °C, 62%. (e) i. TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; ii. Li^0, NH_3, THF, −78 °C, 87%; iii. PPh_3, imid., I_2, THF, 0 °C to room temperature, 91%. (f) **13**, *s*-BuLi, THF, −78 °C, then **11**, −78 °C to room temperature, 38%. (g) i. Et_2AlCl, CH_2Cl_2, −78 °C to room temperature; ii. Bu_4NF, THF, rt, 55% (two steps).

Scheme 2



Scheme 3



+12.3 (c = 0.15 $CHCl_3$), lit.[1] $[\alpha]^{25}_D$ = +15.2 (c = 0.3 $CHCl_3$), lit.[2] $[\alpha]^{25}_D$ = +13 (c = 0.17 $CHCl_3$)}.

In summary, an efficient total synthesis of (+)-testudinariol A was accomplished by employing an asymmetric anti aldol reaction, a new nickel-catalyzed allenyl aldehyde cyclization, and a two-directional oxocarbenium ion/vinyl silane condensation as key steps. The new reactions and methodological advances developed in this total synthesis effort should be broadly useful in various applications.

Acknowledgment. We thank the National Institutes of Health (GM 57014) for support of this research. We also thank Dr. Mohamad Ksebati for assistance with NMR experiments and Professor Christopher Hadad (The Ohio State University) and Dr. Lew Hryhorczuk for mass spectral data.

Supporting Information Available: Full experimental details and copies of NMR spectral data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Spinella, A.; Mollo, E.; Trivellone, E.; Cimino, G. *Tetrahedron* **1997**, *53*, 16891.
(2) (a) Takikawa, H.; Yoshida, M.; Mori, K. *Tetrahedron Lett.* **2001**, *42*, 1527. (b) Yoshida, M.; Takikawa, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1007.
(3) Hioki, H.; Hamano, M.; Kubo, M.; Uno, T.; Kodama, M. *Chem. Lett.* **2001**, 898.
(4) (a) Abiko, A.; Liu, J.-F.; Masamune, S. *J. Am. Chem. Soc.* **1997**, *119*, 2586. (b) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978.
(5) (a) Overman, L. E.; Castañeda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (b) Casteñeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695. (c) Blumenkopf, T. A.; Overman, L. E. *Chem. Rev.* **1986**, *86*, 857.
(6) (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098. (c) Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **2000**, *122*, 6950.
(7) Details of this new procedure will be reported elsewhere.
(8) For a related nickel-catalyzed enone/allene cyclization, see: Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139.
(9) Okamoto, S.; Subburaj, K.; Sato, F. *J. Am. Chem. Soc.* **2001**, *123*, 4857.
(10) (a) Uchida, K.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1976**, *41*, 2215. (b) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739.
(11) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1979**, *44*, 4623.
(12) For other examples of two-directional syntheses, see: (a) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167. (b) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9. (c) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021.

JA027148Y