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

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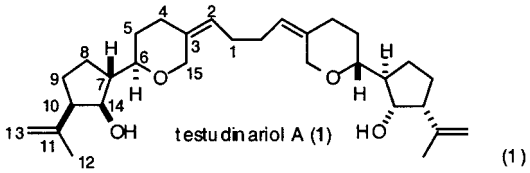
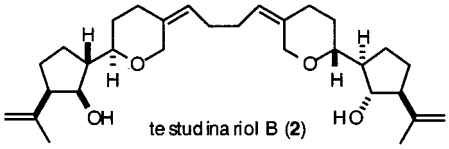
Testudinariols A and B are epimeric triterpene marine natural products that were originally isolated from the skin and the mucus of the marine mollusc *Pleurobranchus testudinarius* by Spinella (eq 1).[1] Testudinariol A (**1**) possesses C_2 symmetry, whereas



(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 {$[\alpha]^{25}_D$ =

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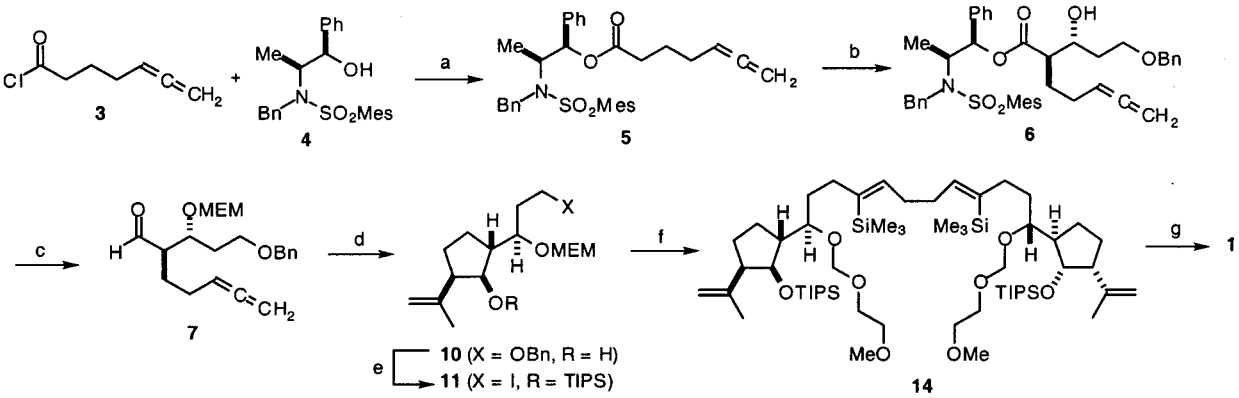
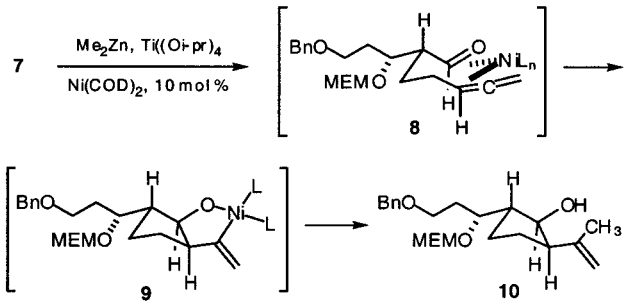
Scheme 1 [a]

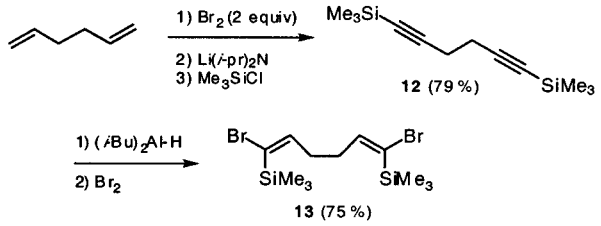


[a] (a) Pyridine, CH_2Cl_2, 0 °C to room temperature, 99%. (b) (*c*-hex)$_2$BOTf, Et_3N, CH_2Cl_2, −78 °C, then HC(O)CH_2CH_2OBn, −78 to 0 °C, 72%. (c) i. $CH_3OCH_2CH_2OCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to room temperature, 79%; ii. $LiAlH_4$, THF, 0 °C, 87%; iii. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −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.

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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.

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