Pergamon

Tetrahedron Letters, Vol. 38, No. 3, pp. 415-416, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02313-1

A Stereoselective Total Synthesis of (±)-Oppositol by a Doubly Diastereoselective Intramolecular Ester Enolate Alkylation

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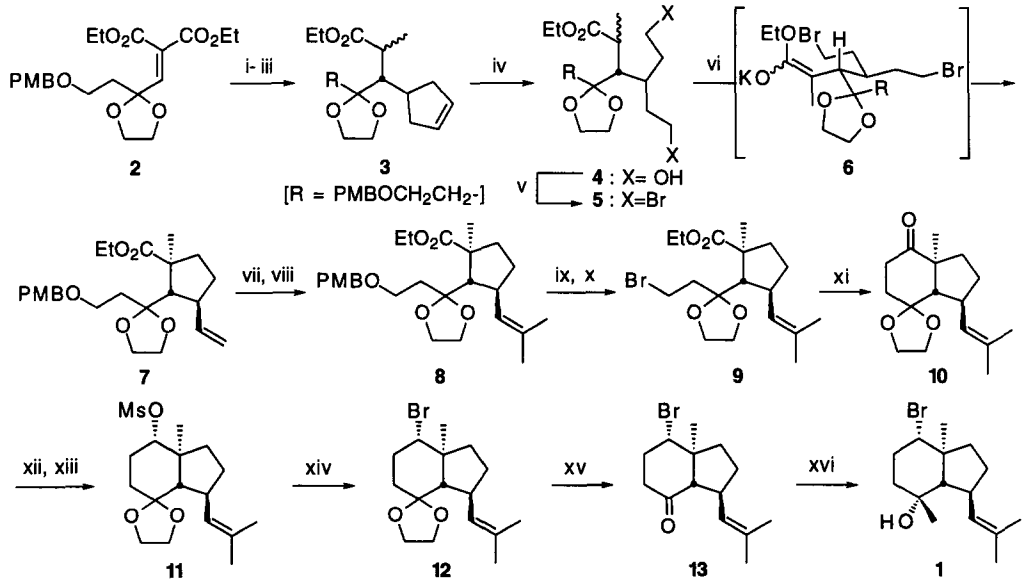
Abstract: The brominated terpene (±)-oppositol (**1**) has been synthesized utilizing a novel doubly diastereodifferentiating *'folding & allylic strain-controlled'* intramolecular ester enolate alkylation.

Oppositol (**1**), an unusual brominated terpene isolated from *Laurentia subopposita* Setchell,[1] has received considerable synthetic attention because of its interesting bicyclic skeleton with five stereogenic centers and unique brominated structure.[2] The first total synthesis of (±)-oppositol (**1**) reported by Masmune *et al.* features a novel acid-catalyzed epimerization of a *cis*-hydrindane system to the corresponding *trans* isomer, and a pivotal Finkelstein reaction for bromine introduction as key steps.[2a] Recently Shibasaki *et al.* prepared an advanced intermediate used in the Masamune synthesis in optically active form by an elegant asymmetric Heck reaction.[2b] Described herein is a stereoselective synthesis of (±)-oppositol (**1**) using a novel doubly diastereodifferentiating *'folding & allylic strain-controlled'*[3] intramolecular ester enolate alkylation(IEEA) as summarized in the scheme below.



Reagents: i) cyclopentenylmagnesium bromide, CuI, THF, -40 to -30 °C, 1.5 h (68%); ii) NaH, MeI, DMF, rt, overnight (94%); iii) NaCN, DMSO, 180 °C, 4 h (76%); iv) a) O_3, CH_2Cl_2, -78 °C, 1.5 h; b) Ph_3P, rt, overnight; c) $NaBH_4$, CH_2Cl_2 -EtOH(1 : 1), 0 °C, 7 h, then rt, 1 h (91%); v) CBr_4, Ph_3P, CH_2Cl_2, 0 °C, 3 h (83%); vi) a) KHMDS, THF, -78 to -25 °C, 3 h; b) *t*-BuOK, THF, 0 °C, 6 h; c) EtI, rt, 12 h (78%); vii) a) O_3, EtOAc, -78 °C, 2 h; b) Ph_3P, rt, overnight (89%); viii) $Ph_3P{=}C(CH_3)_2$, THF, -78 °C, 1 h, then rt, 1 h (93%); ix) DDQ, CH_2Cl_2-H_2O (18 : 1), rt, 1 h (97%); x) CBr_4, Ph_3P, 0 °C, 30 min, then rt, 1 h (94%); xi) *t*-BuLi, ether, -100 to -75 °C, 50 min (72%); xii) $NaBH_4$, 0 °C, 1 h (α : β = 26 : 1; 91%); xiii) MsCl, pyridine, rt, 12 h (90%); xiv) (n-Bu)$_4$NBr, xylene, 155 °C, 18 h (38%); xv) PTSA, acetone, 40 °C, 17 h (93%); xvi) MeLi, ether, -30 to -20 °C, 1 h (95%).

Conjugate addition of cyclopentenylmagnesium bromide[4] to α,β-unsaturated ester **2** in the presence of CuI, methylation of the resulting malonate and decarboethoxylation under Krapcho conditions[5] furnished ester 3 as a mixture of diastereoisomers in 49% overall yield over three steps. Reductive ozonolysis of alkene **3** and subsequent bromination of the resulting diol **4** by the protocol described by Hooz[6] gave the key cyclization substrate **5** in 76% yield for the two steps. Cyclization of dibromo ester **5** with KHMDS in THF followed by *in situ* treatment of the product with potassium *t*-butoxide furnished the desired cyclopentanecarboxylate **7** with excellent stereoselectivity in 78% yield, thereby establishing the relative stereochemistry of the three contiguous chiral centers.[7,8] The observed high stereoselectivity can best be rationalized by considering that the reaction proceeds via *'folding & allylic strain-controlled'* transition state geometry **6** where the preferred *'H-eclipsed'* ester enolate with the bulky side chain appendage in an equatorial position distinguishes the two homomorphic diastereotopic bromoethyl groups.

Ozonolysis of the vinyl group of key intermediate **7** followed by a Wittig reaction with isopropylidenephosphorane produced olefin **8** in 83% overall yield. Removal of the PMB protecting group of **8** with DDQ[9], followed by conversion of the resulting hydroxyl group into the bromide, furnished bromo ester **9** in 91% for the two steps, thus setting the stage for the formation of the second ring by an intramolecular nucleophilic acylation. Thus, upon treatment with *t*-BuLi, ω-bomo ester **9** underwent smooth halogen-metal exchange-initiated INAS[10] to produce *trans*-hydrindane **10** in 73% yield. $NaBH_4$ reduction of ketone **10** and mesylation of the resulting equatorial alcohol gave the correspoding mesylate **11** (82% over two steps), which was subjected to Masamune's bromination conditions[2a] to provide a 38% yield of the desired equatorial bromide **12** and 14% of the corresponding axial bromide, along with a 22% yield of the elimination product.[8,11] Removal of dioxolane group of compound **12** with PTSA in acetone, followed by stereoselective additon of MeLi to the resulting bromo ketone **13**, produced (±)-oppositol (**1**) in 88% overall yield for the two steps. ^{1}H NMR data of the synthetic (±)-oppositol (**1**) were in good agreement with those kindly provided by Professor Masamune.[12]

In summary, a stereoselective synthesis of (±)-oppositol (**1**) has been accomplished in 16 steps from starting material **2** based upon a novel doubly diastereoselective IEEA strategy. Efforts are being made to apply this strategy to syntheses of other natural products.

Acknowledgment: We gratefully acknowledge financial support from the Korea Research Foundation (Non-Directed Research Fund 1966) and OCRC. One of us (I. H. Kim) wishes to thank the Dae Woo Foundation for a fellowship.

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7. The reaction mixture was treated *in situ* with ethyl iodide to recover the hydrolyzed product which was formed to some extent(10 to 15%) during the elimination reaction with potassium *t*-butoxide.
8. All new compounds exhibited satisfactory spectroscopic data. The ratio of isomers was determined by rigorous analysis of 500 MHz ^{1}H NMR spectra. (±)-Oppositol (**1**): **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 16.3, 18.1, 25.7, 28.5, 30.7, 31.2, 36.5, 40.4, 42.9, 47.8, 60.8, 65.3, 71.8, 128.9, 131.9.
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11. The axial bromide could be recycled into the desired equatorial bromide under comparable conditions.
12. We thank Professor A. Murai (Hokkaido University) for sending us a copy of the ^{1}H NMR spectrum of (±)-oppositol (**1**) on behalf of Professosr T. Masamune.

(*Received in Japan* 14 *October* 1996; *revised* 18 *November* 1996; *accepted* 22 *November* 1996)