Pergamon

Tetrahedron Letters 41 (2000) 2189–2192

TETRAHEDRON LETTERS

Facile construction of the lathyrane-type framework via Cr–Ni-mediated cyclization as a key step

Tomoo Matsuura,[a] Shosuke Yamamura [a,*] and Yukimasa Terada [b]

[a]*Department of Chemistry, Faculty of Science and Technology, Keio University, Yokohama, 223-8522, Japan*
[b]*Faculty of Pharmacy, Meijo University, Nagoya, 468-8503, Japan*

Received 17 December 1999; revised 11 January 2000; accepted 14 January 2000

Abstract

A tricyclic compound (**1**) that has a lathyrane-type framework was designed as a model compound of the key intermediate of some diterpenes from *Euphorbiacea* and *Thymeleacea*. Two fragments **2** and **3** were derived from commercially available methyl cyclopentanone-2-carboxylate and (+)-3-carene, respectively. These fragments were coupled by a Cr(II)–Ni(II)-mediated reaction, followed by cyclization under the same conditions to afford **1** in moderate yield. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: cyclization; terpenes and terpenoids; medium-ring carbocycles.

A variety of diterpenes with a unique structure have been isolated from the plants of *Euphorbiacea* and *Thymeleacea* species. The key intermediate of these skeletons is a lathyrane-type skeleton.[1] Some other skeletons, jatrophane, jatrapholane and tigliane seem to be derived from this framework[2] as shown in Scheme 1. Therefore, development of a facile, convenient route for the synthesis of the lathyrane skeleton provides us with a new strategy for other diterpenes via framework transformation. We have reported some transformation reactions to tigliane and jatrapholane frameworks from the lathyrane skeleton.[3]

We report herein a new route to the construction of the lathyrane-type framework. We designed a model compound **1**, which has functional groups necessary for skeletal transformation.

The retrosynthetic route is shown in Scheme 2. Compound **1** seems to be derived from **2** containing a five-membered ring and **3** containing a three-membered ring. Both **2** and **3** could be derived from commercially available methyl cyclopentanone-2-carboxylate, and (+)-3-carene, respectively.

Synthesis of **2** is shown in Scheme 3. Methyl cyclopentanone-2-carboxylate was converted to triflate **4**,[4] followed by Sonogashira coupling reaction with methyl acetylene to give **6**.[5] This compound was further derived to **9** in three steps and subjected to *cis*-specific stannylcupration under Oehlschlager's conditions to give dienyl stannane **10**.[6] Under these conditions, regioselectivity of this reaction was approximately 3:1 for the desired product. The byproduct via *trans* addition was not observed.

* Corresponding author. Tel: +00 81 45 563 1141; fax: +00 81 45 563 5967; e-mail: yamamura@chem.keio.ac.jp (S. Yamamura)

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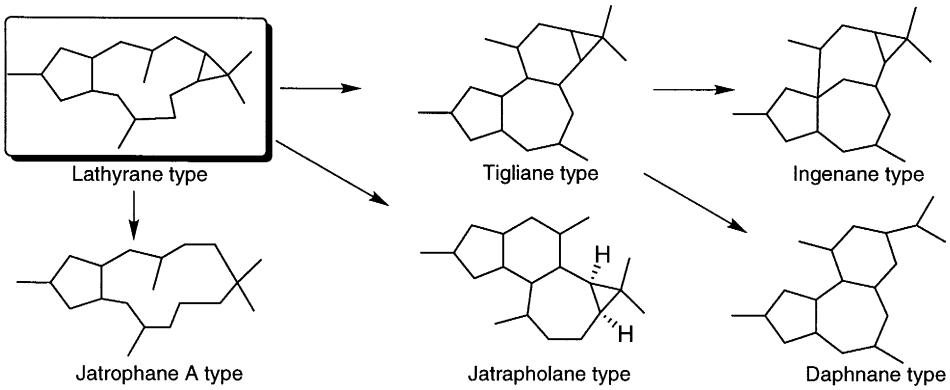
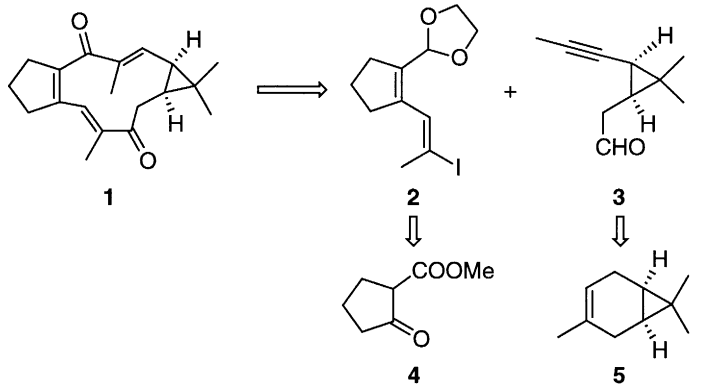
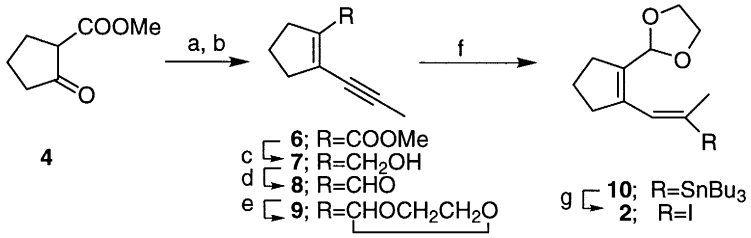
PII: S0040-4039(00)00133-7



Scheme 1. Adolf–Hecker postulate of biosynthesis of diterpenes from *Euphorbiacea*



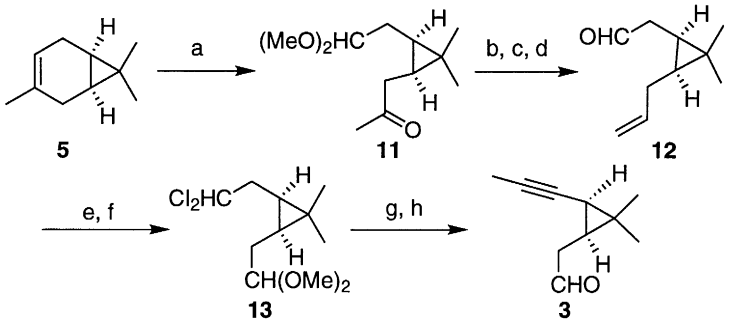
Scheme 2. Synthetic plan of model compound **1**



Scheme 3. Reagents and conditions: (a) Tf_2O (1.0 equiv.), Et_3N (1.0 equiv.), CH_2Cl_2, −78°C, 0.5 h, 95%; (b) $Pd(PPh_3)_4$ (0.3 mol%), CuI (5 mol%), MeCCH (10 equiv.), tol., rt, 2.5 h, 97%; (c) DIBAL-H (2.1 equiv.), tol., −78°C, 1.5 h, 95%; (d) Swern oxd., 88%; (e) $HOCH_2CH_2OH$ (8.0 equiv.), PPTS (1 mol%), PhH, reflux, 4.5 h, 82%; (f) $n Bu_3SnCu(nBu)CNLi_2$ (3.0 equiv.), THF, −78°C, 0.5 h, then MeOH, 78% (3:1); (g) I_2 (1.0 equiv.), Et_2O, 0°C, 30 min quant.

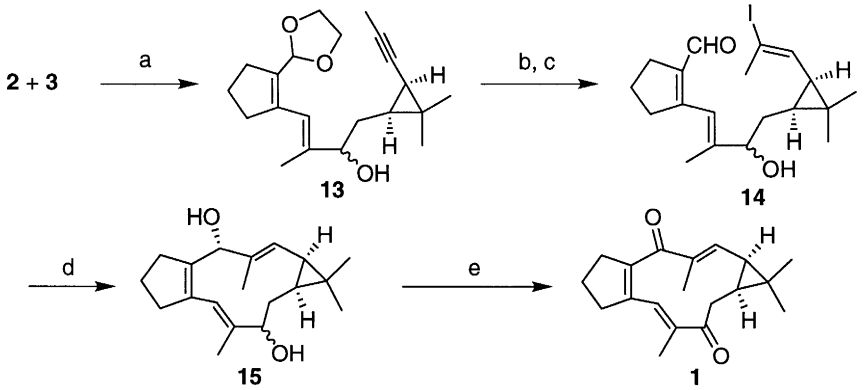
The synthesis of the fragment **3** is shown in Scheme 4. Ozonolysis of (+)-3-carene gave the known ketone **11**.[7] This compound was derived to aldehyde **3** in seven steps. (8% overall yield from (+)-3-carene.)

Compounds **2** and **3** were coupled with a Cr(II)–Ni(II) reagent[8] to give **13** (Scheme 5). The stereoselectivity of this step was not observed (1:1). The methyl acetylene moiety was treated with Schwaltz's reagent followed by treatment with iodine,[9] then by deprotection to afford **14**. Retreatment of **14** with the Cr(II)–Ni(II) reagent for cyclization afforded 11-membered ring compound **15**. Nevertheless, this compound seems to have significant transannular interaction; Cr(II)–Ni(II) coupling was effective for the



Scheme 4. Reagents and conditions: (a) O_3, MeOH, −78°C then Me_2S, TsOH, 81%; (b) $TsNHNH_2$, PhH:MeOH (1:1), rt, 30 min; (c) *n*BuLi (2.1 equiv.), Et_2O, 0°C, overnight; (d) $HClO_4$, THF–H_2O, rt, 4 h, 53% in three steps; (e) PCl_5 (2.0 equiv.), *n*-hexane, 0°C, 15 min; (f) O_3, MeOH, −78°C, then Me_2S, TsOH, 40% in two steps; (g) *n*BuLi (3.2 equiv.), THF:Et_2O (1:1), −78°C to rt then MeI, 68%; (h) $HClO_4$, (cat.), THF–H_2O, rt, 1 day, 70%

construction of the lathyrane-type framework. Compound **15** was treated with IBX[10] to give rise to the target compound (**1**).[11]



Scheme 5. Reagents and conditions: (a) $CrCl_2$ (4.0 equiv.), $NiCl_2$ (5 mol%), DMF, rt, 3 h, 48%; (b) $LiEt_3BH$ (1.0 equiv.) followed by $Cp_2Zr(H)Cl$ (2.1 equiv.), 50°C, 1 h, then I_2, 68%; (c) Et_2O–10% HCl aq., 0°C, 15 min, quant.; (d) $CrCl_2$ (10 equiv.), $NiCl_2$ (1 mol%), DMSO, rt, overnight, 43%; (e) IBX (1.0 M solution in DMSO, 2.0 equiv.), CH_2Cl_2, 2 h, 82%

The conformation of **1** is determined by observation of NOE as shown in Fig. 1. Molecular mechanics calculation of **1a** indicated that this conformer is much stabilized as compared with the other conformer (**1b**).[12] Conformer **1a** is the same as that of the lathyrane-type natural product.

As a result, we were able to establish a new synthetic route to the lathyrane framework using Cr(II)–Ni(II) coupling reaction as the key-step. Compound **1** is a versatile intermediate of jatrapholane and tigliane frameworks via transannular cyclization and we are developing transformation reactions for syntheses of diterpenes including phorbol, ingenol and others.

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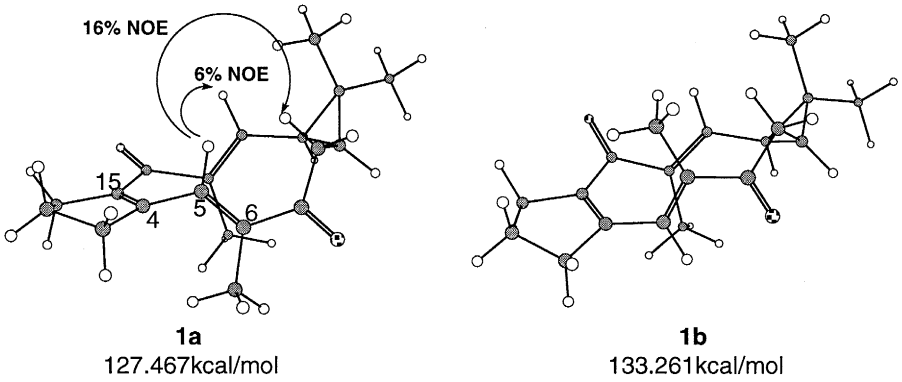

Fig. 1. Two conformers of cyclization product **1**

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11. Spectral data for **1**: ^{1}H NMR ($CDCl_3$ 400 MHz) δ 7.02 (1H, br s), 5.71 (1H, dd, J=1.5, 9.8 Hz), 0.31 (1H, dd, J=11.7, 12.2 Hz), 2.80–2.65 (3H, complex), 2.59 (1H, m), 2.46 (1H, dd, J=4.4, 12.2 Hz), 1.93 (2H, m), 1.67 (3H, d, J=1.5 Hz), 1.66 (3H, d, J=2.0 Hz), 1.31 (1H, dd, J=9.3, 9.8 Hz), 1.11 (3H, s), 1.06 (1H, ddd, J=4.4, 9.3, 11.7 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.0, 197.5, 148.3, 142.3, 140.8, 138.8, 137.3, 131.3, 38.3, 34.6, 33.7, 28.4, 28.3, 26.1, 22.2, 20.7, 15.7, 14.6, 13.2. IR (NaCl, neat) 2951, 1651, 1613 cm^{-1}. HRMS calcd for $C_{19}H_{24}O_2$: 284.1775. Found 284.1795. $[\alpha]_D^{21}$ ($CHCl_3$, c=1.0) −479°.
12. Molecular mechanics calculations were carried out using the MM2/MMP2 molecular modeling program. The effect of conjugated π-orbital systems was taken into consideration. The starting geometry of **1a** and **1b** conformers of each compound was generated by using the program COORD with bond length, bond angles, and torsional angles obtainable from Dreiding molecular models. Iterative calculations were made to minimize the steric energy of each conformer until the energy converged within 0.0039 kcal/mol Å. Subsequently, the torsion angle C15–C4–C5–C6 was driven from 40° to 180° (**1a** conformer) or −40° to −180° (**1b** conformer) at a 10° step using the Tortional Driver option of MM2. The activation energy of the inversion of the C_5=C_6 bond was estimated by the energy difference between the maximum and the minimum. All calculations were performed on a FACOM M-180 at Nagoya University Computation Center: MM2/MMP2: Burkert, U.; Allinger, N. L. *Molecular Mechanics*, ACS Monograph 177, American Chemical Society: Washington, DC, 1982; QCPE #691. COORD: Rhee, J., COORD program, QCPE, #226.