Chinese Chemical Letters 26 (2015) 238–242

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

A facile approach to tricyclo[6.4.0.0^{4,9}]-dodecane framework

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ARTICLE INFO

Article history:
Received 17 August 2014
Received in revised form 6 October 2014
Accepted 21 October 2014
Available online 10 November 2014

Keywords:
Tricyclo[6.4.0.0^{4,9}]dodecane
Vinigrol
Robinson annulation
Bicyclo[3.3.1]nonane

ABSTRACT

The unusual tricyclo[6.4.0.0^{4,9}]dodecane framework was constructed in eight linear steps in 13% overall yield. An innovative strategy accessing the framework from bicyclo[3.3.1]nonanes was employed. The key steps involve a Robinson annulation, a base induced decarboxylation and epimerization in a single step, and an intramolecular alkylation.

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1. Introduction

Tricyclo[6.4.0.0^{4,9}]dodecane framework represents a very unusual ring skeleton that features an unprecedented 1,5-ethano-bridged *cis*-decalin. Although the ring system is rarely found in biological active natural products, its homologue, with two extra CH_2 groups, is represented in the famous natural product, vinigrol (Scheme 1) [1–3]. From the synthetic perspective, the skeleton of vinigrol (**1**) could be built by a two-carbon ring expansion strategy from the tricyclo[6.4.0.0^{4,9}]dodecane framework (**2**) (Scheme 1).

Due to the unique structural feature of the framework, it has received some attention from both synthetic [4–7] and theoretical points of view [8]. Although it is relatively small in size, the presence of four contiguous stereocenters and the unusual carbon ring arrangement make it a challenging synthetic problem, which can be analyzed from several seemingly different topological viewpoints (Scheme 2). Indeed, there is only one report [4] capable of preparing the framework as a byproduct in a very low isolated yield starting from furanophane (furanophane is not commercially available, for the preparation, please see references [9–12]). Herein, we disclose a general and facile synthesis of the skeleton from commercially available starting material.

2. Experimental

Preparation of compound **15**: To an ice-cold solution of the ketone **14** (3.0 g, 14.4 mmol) in 70 mL of dry CH_2Cl_2 was added 2,6-lutidine (6.17 g, 57.6 mmol) and TBSOTf (8.37 g, 31.7 mmol) sequentially, dropwise and the resulting reaction mixture was stirred at r.t. for 3 h. Then the mixture was poured into 100 mL of saturated aqueous $NaHCO_3$ at 0 °C. The solution was extracted thoroughly with CH_2Cl_2, and the organic extracts were dried over Na_2SO_4 and filtered. Removal of the solvent under reduced pressure followed by column with hexane as the eluent to give the doubly TBS protected product (5.6 g, 89%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.72–5.82 (m, 1H), 4.97–5.06 (m, 2H), 2.54–2.57 (m, 1H), 2.39–2.44 (m, 1H), 2.23–2.28 (m, 1H), 2.02–2.14 (m, 2H), 1.60–1.70 (m, 2H), 1.50–1.55 (m, 8H), 1.18–1.21 (m, 1H), 0.96 (s, 9H), 0.87 (s, 9H), 0.15 (d, 6H, J = 6 Hz), 0.08 (d, 6H, J = 7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 138.8, 115.1, 114.2, 74.3, 48.5, 46.3, 38.5, 36.2, 30.1, 25.9, 20.0, 19.4, 18.2, 18.1, 14.8, −1.8, −1.9, −3.6, −3.8. HRMS (ESI-TOF): m/z calcd. for ($C_{25}H_{48}O_2Si_2$+H$^+$): 437.3266; found: 437.3260.

A solution of the above product (4.34 g, 9.9 mmol) in 8.8 mL of THF was cooled to 0 °C, and a solution of 9-BBN in THF (0.5 mol/L, 19.8 mL, 9.9 mmol) was added dropwise under nitrogen. The solution was slowly (about 2 h) warmed to r.t. and stirred for 3 h at r.t. (the reaction was judged complete by TLC). The reaction mixture was opened to air and NaOH solution (3 mol/L, 19.8 mL, 59.4 mmol) was added. The mixture was cooled to 0 °C and H_2O_2 (8.5 mL, 30% max., 79 mmol) was added dropwise followed by MeOH (5.6 mL). The resulting mixture was warmed to r.t. and

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http://dx.doi.org/10.1016/j.cclet.2014.11.003
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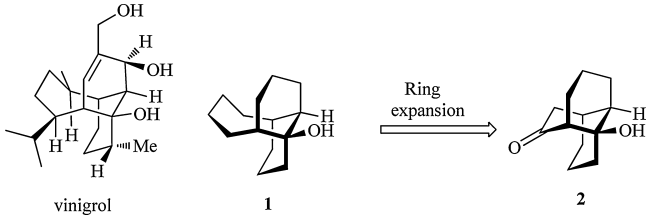
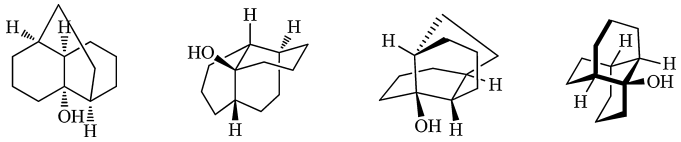


Scheme 1. A ring-expansion approach to vinigrol.



Scheme 2. Different views of tricyclo[6.4.0.0^{4,9}]dodecane framework.

stirred for an additional 3 h. Then the organic solvent was moved in vacuo, and the residue was diluted with ethyl acetate and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated and purified by silica gel chromatography (Hex/EA = 5:1) to give the product **15** (4.47 g, 99%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.60–3.69 (m, 2H), 2.40–2.41 (m, 1H), 2.33–2.37 (m, 2H), 1.75–1.80 (m, 4H), 1.40–1.54 (m, 10H), 0.96 (s, 9H), 0.86 (s, 9H), 0.14 (d, 6H, J = 6 Hz), 0.07 (d, 6H, J = 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.4, 142.3, 114.0, 109.8, 75.2, 74.6, 63.5, 49.1, 48.5, 46.5, 43.5, 43.2, 41.0, 39.3, 36.2, 31.5, 28.4, 25.9, 22.8, 21.2, 20.3, 19.3, 18.2, 15.2, 14.9, −1.8, −3.7. HRMS (ESI-TOF): m/z calcd. for ($C_{25}H_{50}O_3Si_2$+H$^+$): 455.3371; found: 455.3360.

Preparation of compound **16**: To a solution of the alcohol **15** (4.47 g, 9.8 mmol) in 65 mL of THF at −78 °C was added a solution of TBAF (1.0 mol/L, 10 mL, 10.0 mmol) in THF. Then the reaction mixture was increased to 0 °C and stirred for 1.5 h, and then quenched with water. The mixture was then extracted with ethyl acetate and the combined organic phases were washed with brine, dried ($MgSO_4$), filtered and concentrated. Column chromatography (Hex/EA = 3:1) afforded the product **16** (2.8 g, 84%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.70 (t, 2H, J = 5 Hz), 2.64–2.68 (m, 2H), 2.40–2.58 (m, 2H), 2.37–2.38 (m, 1H), 1.85–1.87 (m, 2H), 1.73–1.76 (m, 2H), 1.45–1.56 (m, 5H), 1.10–1.30 (m, 1H), 1.08 (d, 3H, J = 7 Hz), 0.86 (s, 9H), 0.08 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4, 76.0, 63.0, 57.0, 50.0, 48.9, 41.0, 38.8, 34.8, 31.3, 27.3, 25.7, 21.9, 19.4, 18.8, 18.0, 11.8, −1.9. HRMS (ESI-TOF): m/z calcd. for ($C_{19}H_{36}O_3Si$+Na$^+$): 363.2326; found: 363.2332.

Preparation of compound **17**: To a stirred solution of the ketone **14** (1.23 g, 5.9 mmol) in 100 mL of dichloromethane/diisopropyl ethylamine (1:1) at 0 °C was added dropwise MOMCl (4.5 mL, 59 mmol). After stirring 24 h at r.t., the reaction mixture was diluted with 50 mL of DCM and the organic layer was washed with 50 mL of 3 mol/L HCl. The aqueous washes were back extracted with DCM (3× 50 mL), and the combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel (Hex/EA = 10:1) yielded the titled compound **17** (1.08 g, 73%) as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76–5.83 (m, 1H), 5.05–5.12 (m, 2H), 4.79 (d, 1H, J = 7.0 Hz), 4.70 (d, 1H, J = 7.0 Hz), 3.37 (s, 3H), 2.71–2.79 (m, 1H), 2.60–2.68 (m, 2H), 2.36–2.39 (m, 1H), 2.09–2.22 (m, 2H), 1.48–1.75 (m, 6H), 1.20–1.33(m, 1H), 1.08 (d, 3H, J = 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.9, 137.2, 116.5, 89.9, 78.2, 55.4, 53.3, 48.7, 46.6, 38.9, 30.8, 21.9, 20.0, 18.9, 13.2. HRMS (ESI-TOF): m/z calcd. for ($C_{15}H_{24}O_3$+Na$^+$): 275.1618; found: 275.1630.

Preparation of compound **18**: Borane-tetrahydrofuran (1.0 mol/L in THF, 0.46 mL, 0.46 mmol) was placed in a dry, nitrogen-flushed, round-bottomed flask, which was then immersed in an ice-water bath. Cyclohexene (0.093 mL, 0.92 mmol) was added dropwise and the mixture stirred at 0 °C for 1 h. The substrate **17** (116 mg, 0.46 mmol) in 0.3 mL of THF was then added to the slurry of dicyclohexylborane in THF. The cooling bath was removed and the mixture stirred for two hours at r.t. Oxidation was achieved by adding $NaBO_3{\cdot}4H_2O$ (0.212 g, 1.38 mmol) and water (0.5 mL) and stirring was continued at r.t. for additional 2 h. The product was extracted into ether (3× 3 mL), dried ($MgSO_4$), filtered and concentrated. The residue was chromatographed on silica gel (Hex/EA = 1:1) yielding the title compound **18** (120 mg, 97%) as colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.70 (d, 1H, J = 7.0 Hz), 4.64 (d, 1H, J = 7.0 Hz), 3.61 (t, 2H, J = 6.0 Hz), 3.29 (s, 3H), 2.56–2.65 (m, 3H), 2.32–2.34 (m, 1H), 2.12 (br s, 1H), 1.80–2.00 (m, 1H), 1.63–1.79 (m, 4H), 1.41–1.45 (m, 4H), 1.15–1.19 (m, 1H), 1.01 (d, 3H, J = 6.8 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 211.9, 89.9, 78.2, 62.5, 55.2, 53.4, 48.7, 46.6, 38.9, 31.4, 30.8, 21.9, 19.0, 18.6, 12.1. HRMS (ESI-TOF): m/z calcd. for ($C_{15}H_{26}O_4$+Na$^+$): 293.1723; found: 293.1730.

Preparation of compound **19**: To dry DCM (28 mL) was added in this order: triphenylphosphine (2.18 g, 8 mmol), imidazole (0.56 g, 8 mmol) and iodine (2.11 g, 8 mmol). A solution of the alcohol **16** (2.35 g, 7 mmol) in 7 mL of dry DCM was added and the mixture was stirred at room temperature for 2 h. Then the solvent was removed in vacuo and the product was purified by passing it through a column (Hex/EA = 20:1) to afford the product **19** (2.9 g, 93%) as pale yellow crystalline solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.20–3.26 (m, 2H), 2.65–2.68 (m, 1H), 2.34–2.49 (m, 2H), 2.11–2.15 (m, 1H), 1.96–1.98 (m, 2H), 1.73–1.85 (m, 3H), 1.46–1.56 (m, 4H), 1.22–1.24 (m, 1H), 1.05 (d, 3H, J = 7 Hz), 0.88 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.9, 76.5, 51.4, 49.2, 42.6, 41.1, 39.1, 32.0, 27.3, 27.3, 25.9, 20.1, 19.0, 11.9, 7.0, −1.8. HRMS (ESI-TOF): m/z calcd. for ($C_{19}H_{35}IO_2Si$+H$^+$): 451.1524; found: 451.1499.

Preparation of compound **20**: The alcohol **18** (94 mg, 0.35 mmol) was dissolved in THF (2.3 mL) and treated with imidazole (59.2 mg, 0.87 mmol) and triphenylphosphine (109.4 mg, 0.42 mmol). The mixture was cooled to 0 °C and iodine (106 mg, 0.42 mmol) was added in two portions (or added portionwise over 10 min). The reaction mixture was stirred at 0 °C for 2.5 h, warmed to ambient temperature and stirred for another 1 h. The reaction mixture was quenched with saturated sodium thiosulphate (0.16 mL) and water (0.33 mL) and then stirred for 30 min at ambient temperature, poured into water (1.6 mL) and extracted with ethyl acetate (2 × 3.2 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (Hex/EA = 5:1) to yield the titled compound **20** (126 mg, 95%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.76 (d, 1H, J = 7.50 Hz), 4.70 (d, 1H, J = 7.50 Hz), 3.36 (s, 3H), 3.19–3.29 (m, 2H), 2.76 (d, 1H, J = 15.0 Hz), 2.65 (d, 1H, J = 15.0 Hz), 2.37–2.40 (m, 1H), 2.14 (br s, 1H), 1.86–2.02 (m, 4H), 1.72–1.74 (m, 2H), 1.48–1.54 (m, 4H), 1.21–1.24 (m, 1H), 1.08 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.6, 90.2, 78.0, 55.4, 53.6, 48.8, 46.6, 39.2, 32.3, 31.6, 27.3, 19.3, 18.8, 12.3, 7.1. HRMS (ESI-TOF): m/z calcd. for ($C_{15}H_{25}IO_3$+Na$^+$): 403.0741; found: 403.0737.

Preparation of compound **21**: To a solution of dry TMP (2,2,6,6-tetramethylpiperidine, 1.14 mL, 6.56 mmol) in 7.0 mL of THF was added n-butyllithium solution (1.6 mol/L, 4.1 mL, 6.56 mmol) slowly at −78 °C under N_2 and increased the temperature to 0 °C. After 15 min stirring at 0 °C, the mixture was cooled to −78 °C. A solution of the substrate **19** (1.97 g, 4.37 mmol) in 27 mL of THF was added dropwise to the mixture at −78 °C, and the resulting mixture was slowly warmed to −15 °C during the next 1 h, and stirring was continued overnight. Saturated aqueous

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