Tetrahedron Letters 54 (2013) 669–671

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

The first stereoselective total synthesis of nicotlactone A

Palakodety Radha Krishna *, Sunchu Prabhakar, Chittela Sravanthi

D-211, Discovery Laboratory, Organic & Biomolecular Chemistry Division, CSIR–Indian Institute of Chemical Technology, Hyderabad 500007, India

ARTICLE INFO

Article history:
Received 3 October 2012
Revised 29 November 2012
Accepted 1 December 2012
Available online 7 December 2012

Keywords:
Nicotlactone A
γ-Lactone
Anti-tobacco-mosaic (ATM) virus activity
Anti-HIV-1 activity
Rychnovsky anology
Intramolecular lactonization

ABSTRACT

Herein we report the first stereoselective total synthesis of nicotlactone A via acid catalyzed acetonide deprotection followed by intramolecular lactonization in one pot as the key step.

Nicotlactone A **1** (Fig. 1), a lignan derivative was recently isolated from the leaves of Nicotiana tabaccum by Yang et al.[1] Number of bioactive compounds such as alkaloids, sesquieterpenes, diterpenoids, phenols, and lignan derivatives[2] were isolated from the Nicotiana tabacum (for e.g. 2–4). Compound **1** showed anti-TMV activity and modest anti-HIV-1 activity. In anti-TMV activity test, the anti-viral inhibition rate of nicotlactone A (**1**) at 20 μM concentration was 58.4%. This shows that nicotlactone A **1** exhibited high anti-TMV activity; its inhibition rate was higher than that of a positive control. As part of our interest in the total synthesis of biologically active lactones using acid catalyzed lactonization[3] we chose nicotlactone A **1** as our next target. Apart from possessing an impressive bioactivity profile, structurally compound **1** is unique due to its sensitive benzylic alcohol moiety and a tertiary stereogenic centre containing the hydroxyl group next to the lactone ketone. Herein we report the first stereoselective total synthesis of nicotlactone A **1**.

The envisaged retrosynthetic strategy for nicotlactone A **1** is delineated in Scheme 1. A linear synthetic strategy was invoked wherein alcohol **5** was conceived as the ideal precursor to **1**. Alcohol **5** upon oxidation–deprotection–lactonization would lead to nicotlactone A **1** in one pot. While alcohol **5** in turn could be accessed from diol **6** involving functional group transformations like Grignard reaction of the aldehyde generated from **6** with commercially available aryl bromide namely 4-bromo-1,2-(methylenedioxy)benzene followed by protection/deprotection reaction sequence. Diol **6** in turn could be accessed from allylic alcohol **7** by Sharpless asymmetric epoxidation and Gilman's reaction of the corresponding epoxide, while allylic alcohol **7** could be obtained from commercially available hydroxy acetone.

Our synthesis (Scheme 2) began from the inexpensive commercially available starting material hydroxy acetone. Accordingly, Wittig olefination ($Ph_3P{=}CHCO_2Et$/benzene/reflux/8 h) of the hydroxyl acetone provided the desired hydroxy ester **8** (92%) as an exclusive *E*-isomer. The alcohol functionality in **8** was protected as its PMB ether {PMBO(C=NH)CCl_3/cat.PTSA/CH_2Cl_2/0 °C to rt/3 h}. Next, α,β-conjugated ester was reduced (DIBAL-H/CH_2Cl_2/0 °C/0.5 h) to the corresponding allylic alcohol **7** (91%). Subsequently, allylic alcohol **7** was converted into chiral epoxy alcohol **10** under Sharpless[4] conditions {(+)-DIPT/Ti(O^iPr)$_4$/TBHP/4 Å MS/CH_2Cl_2/−20 °C/92%}. Furthermore, compound **10** on regioselective ring-opening reaction with Gilman's reagent[5] (Me_2CuLi/Ether/−20 °C/1 h) led to the desired 1,3-diol precursor **6** (85%) as the major isomer. The crude reaction mixture was treated with $NaIO_4$ in THF/H_2O (4:1) in order to eliminate the minor 1,2-diol by an oxidative cleavage. The thus obtained diol **6** constitutes one of the important precursors in this synthesis.

Next, the primary alcohol of compound **6** (Scheme 3) was oxidized under Swern oxidation conditions {$(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/−78 °C} to furnish the corresponding aldehyde which was subjected to Grignard reaction with 4-bromo-1,2-(methylenedioxy)benzene in THF under reflux conditions to afford compound **11** (71%) as a major isomer (dr = 89:11). The ratio was measured by LCMS {column: XDB-C 18, 30% water in acetonitrile, flow rate: 1 mL/min, 254 nm, t_r(major) = 2.814 min, t_r(minor) = 2.339 min}. The stereochemistry of the newly created stereogenic center was assigned based on Rychnovsky's analogy of the corresponding

* Corresponding author. Fax: +91 4027160387.
E-mail address: prkgenius@iict.res.in (P. Radha Krishna).

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http://dx.doi.org/10.1016/j.tetlet.2012.12.003

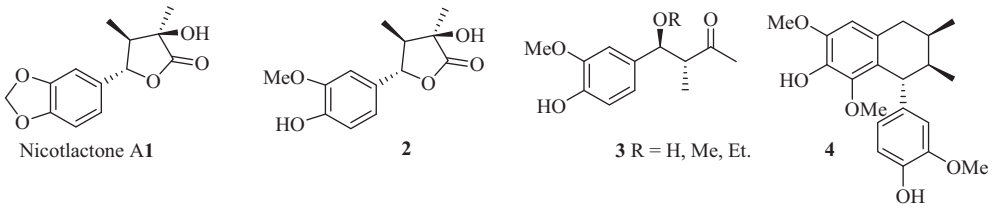
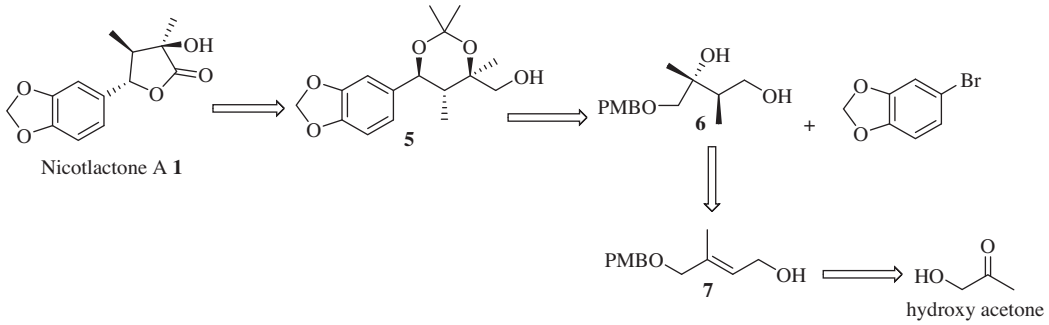
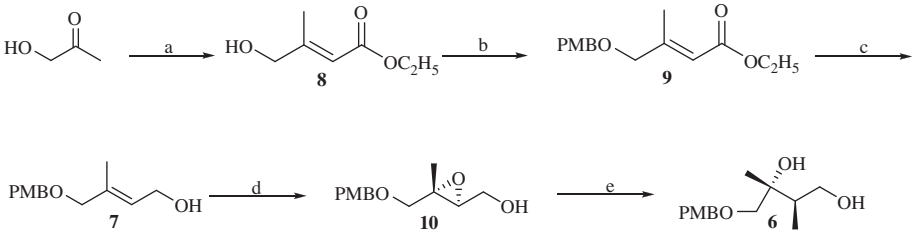


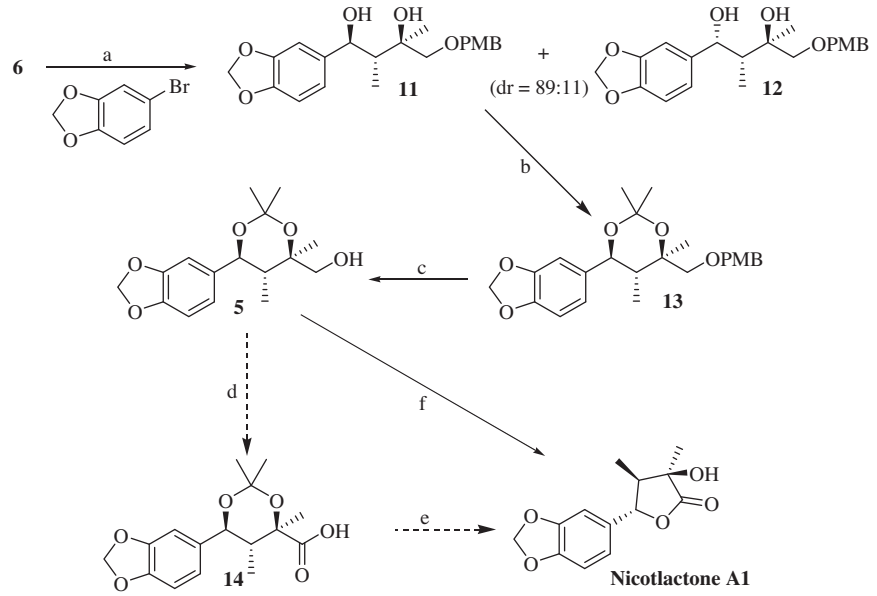
Figure 1. Some lignan derivatives.



Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) $Ph_3P{=}CHCO_2Et$, benzene, reflux, 8 h, 92%; (b) $PMBO(C{=}NH)CCl_3$, PTSA, dry CH_2Cl_2, 0 °C to rt, 3 h, 90%; (c) DIBAL-H, dry CH_2Cl_2, 0 °C, 0.5 h, 91%; (d) (+)-DIPT, $Ti(OiPr)_4$, TBHP, 4 Å MS, dry CH_2Cl_2, −20 °C, 5 h, 92%; (e) (i) Me_2CuLi, dry ether, −20 °C, 1 h, (ii) $NaIO_4$, THF/H_2O (4:1) (over two steps 85%).



Scheme 3. Reagents and conditions: (a) (i) $(COCl)_2$, dry DMSO, Et_3N, dry CH_2Cl_2, −78 °C; (ii) Mg, 4-bromo-1,2-(methylenedioxy)benzene, dry THF, reflux, 1 h, 0 °C, aldehyde, 1 h, 71% (major isomer, over two steps); (b) 2,2-DMP, PPTS, dry CH_2Cl_2, 0 °C to rt,12 h, 90%; (c) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C to rt, 0.5 h, 86%; (d) TEMPO/BAIB, CH_2Cl_2/H_2O (1:1), 0 °C to rt, 2 h; (e) 5 N HCl, THF, reflux; (f) same as d, then while acid workup with 2 N HCl, 75% (over three steps).

acetonide **13**.[6] For instance, the ^{13}C NMR of **13** revealed the carbon atoms due to the acetonide methyls that appeared at δ 19.7 and at δ 31.8 ppm characteristic of the acetonide of a syn-1,3-diol moiety. Thus the relative stereochemistry of the newly created stereogenic center was unequivocally assigned as syn to the existing one and its absolute stereochemistry as 'S'. Then the PMB group of compound **13** was deprotected under standard DDQ oxidation conditions (DDQ/CH_2Cl_2/H_2O/0 °C to rt/0.5 h) to result in alcohol **5** (86%).

Finally, the primary alcohol was oxidized to its carboxylic acid under TEMPO/BAIB conditions. Fortunately the acidic (2 N HCl) work-up, normally adopted after the oxidation step, helped us realize the target compound nicotlactone A **1** (75%) in one pot via sequential reactions such as acetonide deprotection followed by the intramolecular lactonization reactions. By this way the target molecule was achieved in shorter steps than the envisaged stepwise strategy. The data of the synthetic sample matched with the reported values of the natural product.[1,7]

In summary, the first total synthesis of nicotlactone A (24% overall yield) was reported via acid catalyzed intramolecular lactonization of the corresponding hydroxyl protected acid wherein multiple reactions occurred in one step. This strategy may be adopted for the synthesis of similar ring-containing natural products.

Acknowledgments

Two of the authors (S.P. and C.S.) thank CSIR, New Delhi, for the financial support in the form of a fellowship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.003.

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7. *Spectral data of the compounds*: *Compound* ***8***: Pale yellow liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 5.93 (s, 1H), 4.20–4.06 (m, 4H), 2.08 (s, 3H), 1.99 (br s, 1H), 1.29 (t, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.0, 157.4, 113.4, 66.7, 59.7, 15.4, 14.1; LCMS: 167 $[M+Na]^+$. Anal. Calcd for $C_7H_{12}O_3$: C, 58.32; H, 8.39; O, 33.29. Found: C, 58.48; H, 8.25; O, 33.27. *Compound* ***9***: Colorless liquid; ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, 2H, J = 8.4 Hz), 6.84 (d, 2H, J = 8.4 Hz), 5.95 (s, 1H), 4.45 (s, 2H), 4.16 (q, 2H, J = 14.3, 6.9 Hz), 3.93 (s, 2H), 3.81 (s, 3H), 2.11 (s, 3H), 1.31(t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.6, 159.2, 154.5, 131.9, 129.8, 129.2, 115.2, 114.2, 113.8, 73.7, 72.1, 59.6, 55.2, 15.7, 14.2; HRMS m/z: calcd for $C_{15}H_{20}O_4Na$ $[M+Na]^+$: 287.1253; found: 287.1262. *Compound* ***7***: Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 8.4 Hz), 6.88 (d, 2H, J = 8.6 Hz), 5.68 (dt, 1H, J = 6.7, 1.1 Hz), 4.42 (s, 2H), 4.21 (d, 2H, J = 6.6 Hz), 3.90 (s, 2H), 3.81(s, 3H), 1.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 135.3, 130.2, 129.2, 126.1(2), 113.6(2), 75.0, 71.5, 58.8, 55.1, 13.9; HRMS: m/z calcd for $C_{13}H_{18}O_3Na$ $[M+Na]^+$: 245.1148; found: 245.1157. *Compound* ***10***: Colorless liquid; $[\alpha]_D^{25}$ 5.9 (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 2H, J = 8.4 Hz), 6.82 (d, 2H, J = 8.3 Hz), 4.45 (br s, 2H), 3.79 (br s, 4H), 3.72–3.61 (m, 1H), 3.39 (br s, 2H), 3.01 (t, 1H, J = 5.4 Hz), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 129.8, 129.3, 113.8(4), 73.8, 72.9, 60.9, 60.4, 60.0, 55.1, 25.7, 14.5; HRMS m/z: calcd for $C_{13}H_{18}O_4Na$ $[M+Na]^+$: 261.1097; found: 261.1093. *Compound* ***6***: Pale yellow liquid; $[\alpha]_D^{25}$ +12.5 (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, 2H, J = 7.5 Hz), 6.89 (d, 2H, J = 8.6 Hz), 4.50 (q, 2H, J = 16.6, 11.5 Hz), 3.81 (br s, 3H), 3.74 (d, 1H, J = 9.6 Hz), 3.61–3.51 (m, 1H), 3.40 (d, 1H, J = 9.0 Hz), 3.28 (d, 1H, J = 9.0 Hz), 2.97 (br s, 1H), 2.11–1.98 (m, 1H), 1.66 (br s, 1H), 1.14 (br s, 3H), 0.78 (d, 3H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 129.8, 129.2, 113.7(2), 76.1, 75.9, 73.0, 65.5, 55.2, 40.0, 19.2, 12.6; HRMS m/z: calcd for $C_{14}H_{22}O_4Na$ $[M+Na]^+$: 277.1410; found: 277.1407. *Compound* ***11***: Colored oil; $[\alpha]_D^{25}$ −6.2 (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 2H, J = 8.6 Hz), 6.88 (d, 3H, J = 7.9 Hz), 6.75 (dd, 2H, J = 9.8 Hz), 5.93 (s, 2H), 5.14 (br s, 1H), 4.54 (d, 1H, J = 9.0 Hz), 4.45 (d, 1H, J = 11.3 Hz), 3.80 (br s, 3H), 3.41 (d, 1H, J = 9.4 Hz), 3.25 (d, 1H, J = 9.4 Hz), 2.16–2.03 (m, 1H), 1.25 (s, 3H), 0.45 (d, 3H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 147.6, 146.8, 137.6, 129.6, 129.3, 120.9, 113.7(3), 107.6, 107.4, 100.8, 77.6, 76.8, 76.1, 73.0, 60.3, 55.1, 44.4, 29.6, 18.1, 13.3; HRMS m/z: calcd for $C_{21}H_{26}O_6Na$ $[M+Na]^+$: 397.1621; found: 397.1637; LCMS {Column: XDB-C18, 30% water in acetonitrile, flow rate: 1 mL/min, 254 nm, t_r(major) = 2.814 min, t_r(minor) = 2.339 min}. *Compound* ***13***: Pale yellow oil; $[\alpha]_D^{25}$ −16.5 (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, 2H, J = 8.4 Hz), 6.93 (br s, 1H), 6.86 (d, 2H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.1 Hz), 6.77 (d, 1H, J = 7.9 Hz), 5.93 (d, 2H, J = 3.0 Hz), 4.65 (d, 1H, J = 11.8 Hz), 4.54 (d, 1H, J = 8.8 Hz), 4.47 (d, 1H, J = 7.5 Hz), 3.80 (br s, 3H), 3.35 (q, 2H, J = 12.6, 10.7 Hz), 2.16–1.99 (m, 1H), 1.55 (br s, 3H), 1.47 (br s, 3H), 1.29 (br s, 3H), 0.52 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 147.7, 147.2, 134.6, 130.7, 129.1(2), 121.2, 113.6(3), 107.6, 100.8, 98.5, 77.1, 74.2, 73.1, 55.1, 38.8, 31.8, 24.9, 19.7, 12.0; HRMS m/z: calcd for $C_{24}H_{30}O_6Na$ $[M+Na]^+$: 437.1821; found: 437.1816. *Compound* ***5***: Pale yellow oil; $[\alpha]_D^{25}$ −14.5 (c 0.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.93 (d, 1H, J = 1.5 Hz), 6.83 (dd, 1H, J = 1.5 Hz), 6.78 (d, 1H, J = 4 Hz), 5.96–5.93 (m, 2H), 4.53 (d, 1H, J = 10.5 Hz), 3.42–3.31 (m, 2H), 2.23–2.13 (m, 1H), 1.57 (br s, 3H), 1.45 (s, 3H), 1.26 (s, 3H), 0.56 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7, 136.0, 120.5, 107.8, 100.8, 75.1, 71.8, 69.6, 48.5, 31.9, 29.6, 25.3, 22.6, 19.3, 14.0, 11.8; HRMS m/z: calcd for $C_{16}H_{22}O_5Na$ $[M+Na]^+$: 317.1359; found: 317.1368. *Nicotlactone A* ***1***: Pale yellow crude oil; $[\alpha]_D^{25}$ +23.3 (c 0.05, $CHCl_3$); ^1H NMR (500 MHz, CD_3COCD_3): δ 6.97 (br s, 1H), 6.92 (d, 1H, J = 8.1 Hz), 6.85 (d, 1H, J = 8.1 Hz), 6.02 (br s, 2H), 5.01 (d, 1H, J = 9.4 Hz), 4.86 (br s, 1H), 2.19–2.12 (m, 1H), 1.43 (br s, 3H), 1.01 (d, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, CD_3COCD_3): δ 176.1, 147.5, 131.4, 120.5, 107.3, 113.3, 100.8, 83.9, 77.7, 73.4, 48.7, 20.0, 6.3; HRMS m/z: calcd for $C_{13}H_{14}O_5Na$ $[M+Na]^+$: 273.0733; found: 273.0746.