Pergamon

Tetrahedron Letters 39 (1998) 3765–3768

TETRAHEDRON LETTERS

Enantio- and Diastereocontrolled Synthesis of (–)-19(*S*)-Acetoxy-N_1-acetyl-20-epitubifolidine

Kogyoku Shin, Minoru Moriya, and Kunio Ogasawara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

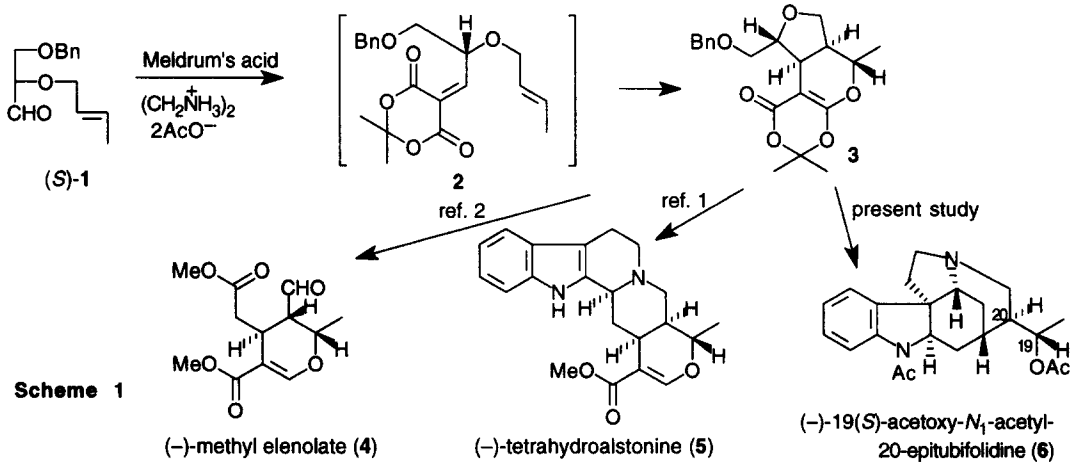
Fax +81-22-217-6845; E-mail konol@mail.cc.tohoku.ac.jp

Received 20 February 1998; accepted 13 March 1998

Abstract: An enantiocontrolled route to the 19-oxygenated pentacyclic *Strychnos* alkaloids has been demonstrated by the stereoselective synthesis of (–)-19(*S*)-acetoxy-N_1-acetyl-20-epitubifolidine.

Keywords: Cyclization; Enantiocontrol; Indolization; Natural products

We found that (*S*)-2-*O*-[(*E*)-but-2-enyl]-3-*O*–benzylglyceraldehyde **1** reacted with Meldrum's acid to give stereoselectively the tricyclic adduct[1,2] **3** *via* the transient intermediate **2** by a tandem Knoevenagel condensation and intramolecular hetero-Diels-Alder reaction.[3] Utilizing **3** as the common chiral building block, a secoiridoid monoterpene (–)-methyl elenolate[2] (**4**) and a *Corynanthe* indole alkaloid (–)-tetrahydroalstonine[1] (**5**) have been prepared. We now wish to report another utility of **3** for the synthesis of (–)-19(*S*)-acetoxy-N_1-acetyl-20-epitubifolidine (**6**) having the pentacyclic *Strychnos* framework[4,5] whose enantiocontrolled construction has not been reported so far (**Scheme 1**).

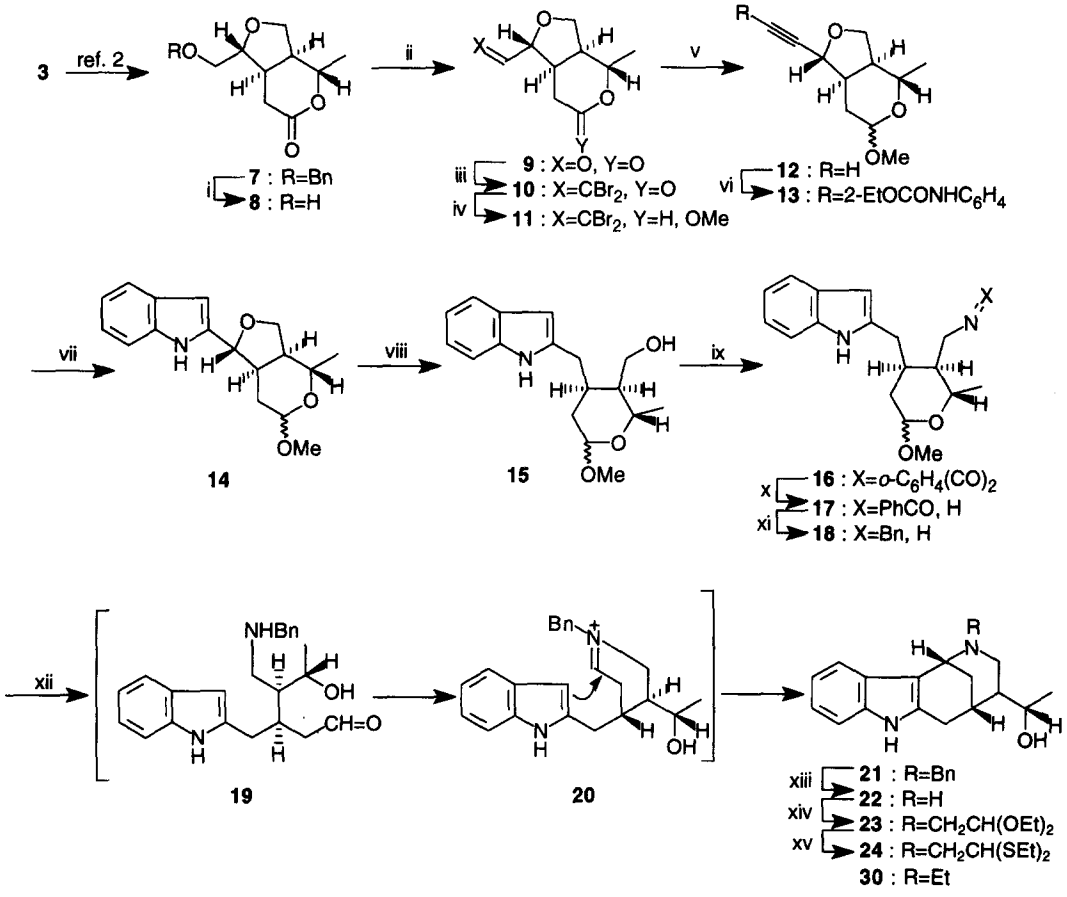


Scheme 1

0040-4039/98/$19.00
PII: S0040-4039(98)00597-8

The bicyclic lactone **7**, obtained in 60% overall yield from **1** *via* **3**, was transformed into the ketene dibromide **10**, mp 140.5-142 °C, $[\alpha]_D^{29}$ -35.4 (*c* 0.8, $CHCl_3$), by sequential debenzylation, Swern oxidation and dibromomethylenation[6] through **8** and **9**. On partial reduction followed by acetalization, **10** gave the acetal **11** (as a 3:2 mixture) which was exposed to butyllithium[6] in THF containing HMPA (2 equiv.) to give the acetylene **12**. Palladium-catalyzed coupling[7] of **12** with *N*-carbethoxy-2-iodoaniline afforded the arylacetylene **13** which, on reflux with sodium ethoxide in ethanol, furnished the 2-substituted indole[8,9] **14**. The benzylic ether bond of **14** was then cleaved by the Birch reduction to generate the alcohol **15** which was transformed into the amine **18** by a five-step reaction including the Mitsunobu reaction[10] through **16** and **17**.

Upon reflux in trifluoroacetic acid, **18** furnished the tetracyclic amine **21**, $[\alpha]_D^{27}$ -186.9 (*c* 1.0, $CHCl_3$), in 90% yield as a single epimer by concurrent formation of the aldehyde **19** and the iminium intermediate **20**. To construct the fifth ring of the target molecule, the *N*-benzyl functionality of **22** was first substituted by the

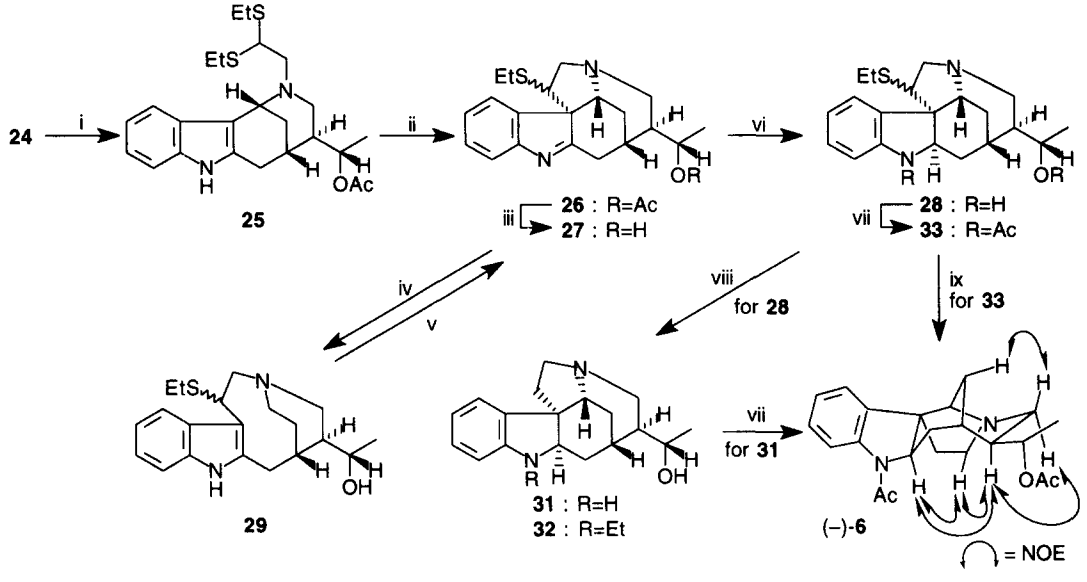


Scheme 2 *Reagents and conditions*: i) H_2, $Pd(OH)_2$, MeOH. ii) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, then Et_3N, -78 °C ~ room temp. iii) CBr_4, PPh_3, CH_2Cl_2, reflux (75% from **4**). iv) (a) DIBAL, CH_2Cl_2, -78 °C. (b) $HC(OMe)_3$, PPTS (cat.), MeOH, reflux (89%). v) *n*-BuLi, HMPA, THF, -78 °C (87%). vi) 2-$IC_6H_4NHCO_2Et$, $PdCl_2(PPh_3)_2$ (2 mol %), CuI (0.5 mol %), Et_3N, room temp. (92%). vii) EtONa, EtOH, reflux (85%). viii) Li, liq. NH_3, -33 °C (86%). ix) PPh_3, phthalimide, diisopropyl azodicarboxylate, THF. x) (a) hydrazine hydrate, EtOH, reflux. (b) BzCl, Et_3N, CH_2Cl_2 (72% from **15**). xi) $LiAlH_4$, dioxane, reflux (86%). xii) CF_3CO_2H, reflux (90%). xiii) 10% Pd-C, HCO_2NH_4, MeOH, reflux. xiv) $BrCH_2CH(OEt)_2$, K_2CO_3, dioxane, reflux (72% from **21**). xv) EtSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C ~ room temp. (71%).

2,2-diethoxyethyl functionality to give **23**, $[\alpha]_D^{27}$ –88.5 (*c* 1.1, $CHCl_3$),*via* **22** by sequential debenzylation and alkylation. Then, **23** was treated with ethanethiol in the presence of boron trifluoride etherate[11] to give the thioacetal **24**, $[\alpha]_D^{27}$ –107.0 (*c* 0.9, $CHCl_3$), in 71% yield, which was accompanied with the pentacyclic indolenine **27** (as a 15:1 mixture) in 10% yield (**Scheme 2**).

However, the thioacetal **24** failed to give **27** under the same conditions as well as under various conditions even with the use of dimethyl(methylthio)sulfonium fluoroborate[11] (DMTSF) which has been employed in the synthesis of the pentacyclic *Strychnos* indole alkaloids without bearing a C19 hydroxy functionality. Eventually, we found that the cyclization took place when the acetate **25**, $[\alpha]_D^{27}$ –80.1 (*c* 1.1, $CHCl_3$), obtained from **24**, was treated with silver nitrate (2 equiv.) and 2,6-lutidine (2 equiv.) followed by NCS in acetonitrile in the presence of molecular sieves (3 Å) and silica gel[12] (230~400 mesh) to furnish the pentacyclic acetate **26** in 44% yield (as a ca. 15:1 mixture), which gave **27** (as a 15:1 mixture) on methanolysis. Reduction of **27** to the indoline **28** was accomplished in 73% yield using $NaBH_3CN$ in methanol at pH 3.0. When $NaBH_4$ in place of $NaBH_3CN$ was used under neutral conditions, **27** furnished the nine-membered indole **29** which reverted to **27** on exposure to oxygen in the presence of Adams catalyst.[13]

Desulfurization of the indolenine **27** was found to be unexpectedly difficult. Treatment of **27** with Raney nickel (W-2) gave a complex mixture,[11] while it with Bu_3SnH[12a] afforded the tetracyclic N_4-ethylindole **30**, $[\alpha]_D^{30}$ –69.0 (*c* 0.2, $CHCl_3$). On the other hand, the desulfurization of the indoline **28** occurred with Raney nickel (W-2) in ethanol,[11] but an inseparable mixture (ca. 1:1) of the 19(*S*)-hydroxy-20-epitubifolidine **31** and its N_1-ethyl derivative **32** was generated. As the mixture was found to be separable after acetylation, the indoline **28** was first acetylated to give the acetamide **33** which then was refluxed with Raney nickel (W-2) in ethanol to give (–)-19(*S*)-acetoxy-N_1-acetyl-20-epitubifolidine[14] (**6**), $[\alpha]_D^{29}$ –60.0 (*c* 0.1, $CHCl_3$), in 86%



Scheme 3 Reagents and conditions: i) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2, 0 °C ~ room temp. (92%). ii) $AgNO_3$, molecular sieves (3Å), SiO_2 (~400 mesh), 2,6-lutidine, MeCN, then NCS (44%). iii) K_2CO_3, MeOH (85%). iv) $NaBH_4$, MeOH (72%). v) O_2, PtO_2, AcOEt (50%). vi) $NaBH_3CN$, cat. HCl, MeOH (pH 3) (73%). vii) Ac_2O, Et_3N, DMAP (cat.), CH_2Cl_2 (100%). viii) Raney Ni (W-2), EtOH, reflux [64% **31** and **32** (1:1)]. ix) Raney Ni (W-2), EtOH, reflux (86%).

yield as a single product. Stereochemistry of **6**, which was existed in two rotamer forms (ca. 1:1), was assigned as shown by ^{1}H NMR analysis (NOESY, COSY, DEPT) (**Scheme 3**).

In conclusion we have devised an extensive utilization of the chiral adduct **3** for the enantiocontrolled construction of the 19-oxygenated pentacyclic *Strychnos* alkaloids and, at the same time, we have made synthetic unification of the *Strychnos* alkaloids and the biogenetically close-related two groups, the secoiridoid monoterpenes and the *Corynanthe* indole alkaloids. Synthetic studies toward natural *Strychnos* alkaloids employing the present procedure are in progress.

REFERENCES AND NOTES

[1] Takano, S.; Satoh, S.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.*, **1988**, 59-60.
[2] Takano, S.; Satoh, S.; Ogasawara, K.; Aoe, K. *Heterocycles*, **1990**, *30*, 583-605.
[3] Tietze , L. F.; Beifuss, U. Comprehensive Organic Synthesis, ed. B. M. Trost, Pergamon, Oxford, **1991**, Vol. 2, pp. 341-394.
[4] A pertinent review, see: Bosch, J.; Bonjoch, J.; Amat, M. The Alkaloids, ed. G. A. Cordell, Academic Press, San Diego, **1996**, Vol. 48, pp. 75-189.
[5] Saxton, J. E.; *Nat. Prod. Rep.*, **1997**, *14*, 559 and the former reports.
[6] Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.*, **1972**, 3769-3772.
[7] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.*, **1975**, 4467-4470.
[8] Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles*, **1986**, 24, 31-32.
[9] Utilization of this procedure for the natural product synthesis: Takano, S.; Sato, T.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.*, **1991**, 462-464. Shin, K.; Ogasawara, K. *Chem. Lett.*, **1995**, 289-290. Shin, K.; Ogasawara, K. *Synlett*, **1995**, 859-860. Shin, K.; Ogasawara, K. *Synlett*, **1996**, 922-924. Saito, M.; Kawamura, M.; Hiroya, K.; Ogasawara, K. *Chem. Commun.*, **1997**, 765-766.
[10] Mitsunobu, O. *Synthesis*, **1981**, 1-28. Hughes, D. L. Organic Reactions, **1992**, *42*, 335-656. Hughes, D. L. *Org. Prep. Proced. Int.*, **1996**, *28*, 127-164.
[11] Bosch, J.; Amat, M. *Tetrahedron Lett.*, **1985**, *26*, 4951-4954. Amat, M.; Linares, A.; Salas, M. -L.; Alvarez, M.; Bosch, J. *J. Chem. Soc. Chem. Commun.*, **1988**, 420-421. Amat, M.; Linares, A.; Bosch, J. *J. Org. Chem.*, **1990**, *55*, 6299-6312. Gracia, J.; Bonjoch, J.; Casamitjana, N.; Amat , M.; Bosch, J. *J. Chem. Soc., Chem. Commun.*, **1991**, 614-615. Gracia, J.; Casamitjana, N.; Bonjoch, J.; Bosch, J. *J. Org. Chem.*, **1994**, *59*, 3939-3951.
[12] (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. -K. *J. Am. Chem. Soc.*, **1986**, *108*, 2468-2469. (b) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C. -K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.*, **1989**, *111*, 5321-5330.
[13] Schumann, D.; Schmid, H. *Helv. Chim. Acta*, **1963**, *46*, 1996-2003.
[14] All new compounds described have satisfactory spectral (IR, ^{1}H NMR, MS) and analytical (HRMS) data. For the compound (–)-**6**: IR (cm^{-1}): n=1731, 1655; ^{1}H NMR (300 MHz, $CDCl_3$): d=1.22 (d, 1.5H, *J*=6.3 Hz), 1.23 (d, 1.5H, *J*=6.3 Hz), 1.12-2.62 (m, 9H), 2.03 (s, 1.5H), 2.06 (s, 1.5H), 2.32 (s, 1.5H), 2.43 (s, 1.5H), 2.82-3.09 (m, 2H), 3.30-3.48 (m, 1H), 3.85 (br d, 1H, *J*=14.6 Hz), 4.09 (dd, 0.5H, *J*=10.7, 7.1 Hz), 4.66 (dd, 0.5H, *J*=10.9, 7.1 Hz), 4.72-4.87 (m, 1H), 7.05-7.32 (m, 3.5H), 8.17 (d, 0.5H, *J*=8.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): d =170.9, 170.8, 168.2, 168.1, 141.9, 141.1, 136.5, 134.1, 128.4, 128.0, 124.6, 124.1, 123.3, 122.0, 118.3, 115.4, 72.8, 72.7, 63.4, 62.4, 58.4, 58.1, 52.3, 51.8, 51.7, 50.9, 47.3, 47.0, 40.7, 40.4, 38.5, 38.2, 36.8, 35.4, 29.8, 25.7, 25.5, 24.3, 23.8, 23.5, 23.4, 21.3, 17.8, 17.6; MS: 368 (M^+), 196 (100 %); HRMS: Calcd for $C_{22}H_{28}N_2O_3$: 368.2100. Found: 368.2084.