SYNTHESIS OF 2-AZA-4-KETOPODOPHYLLOTOXIN

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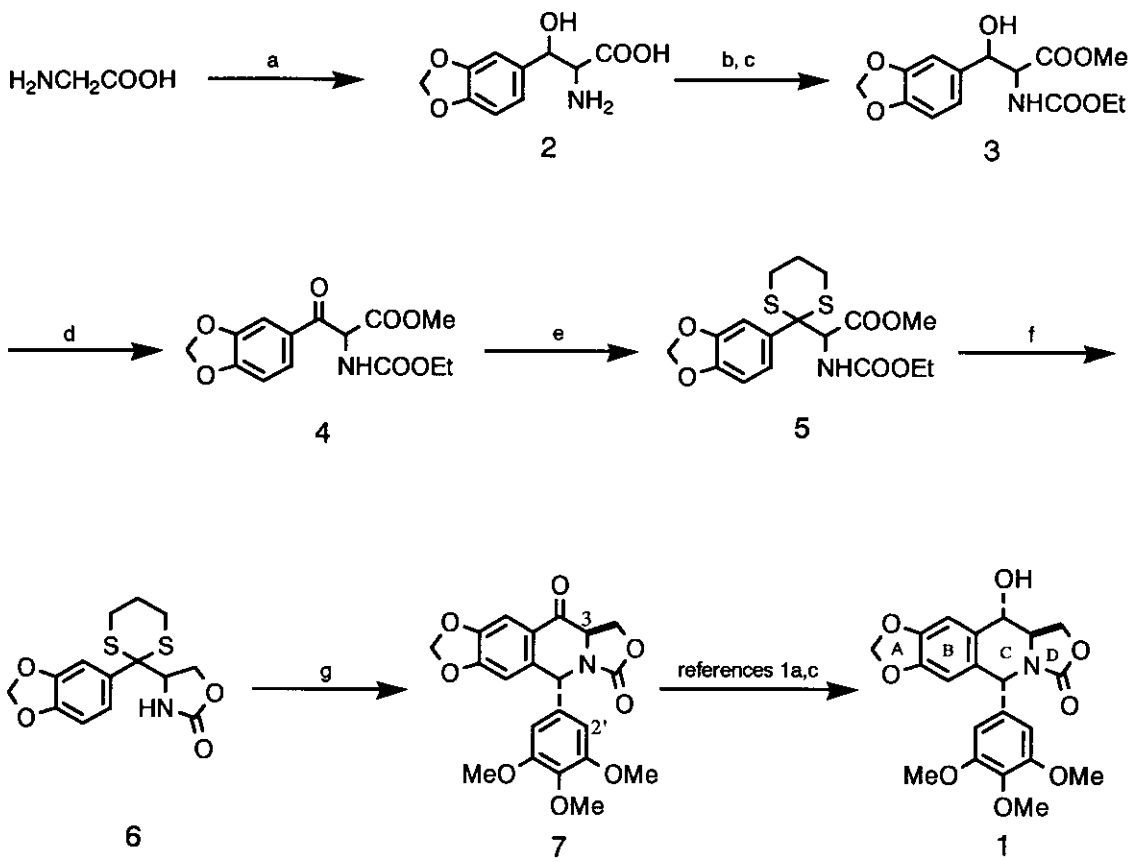
Abstract - A synthesis of 2-aza-4-ketopodophyllotoxin (7), a key intermediate of 2-azapodophyllotoxin (1), is reported.

2-Azapodophyllotoxin analogues have recently receieved much attention because of not only those structual similarities to podophyllotoxin, but also their promising biological properties.[1] In the present communication, we report a facile synthesis of 2-aza-4-ketopodophyllotoxin (7) which can be converted to 2-azapodophyllotoxin (1) in one step.

Our strategy is characterized by making use of the functionalities of methylenedioxy-DOPS (2) (mp 163-167° C, decomp.), which is readly prepared by the condensation of glycine with 2.0 equiv. of piperonal in ethanolic alkaline solution in 64% yield.[2,3] Treatment of 2 with ethyl chloroformate followed by methylation with dimethyl sulfate afforded a 83 % yield of 3 (mp 113-117°C). Oxidation of the benzylic hydroxyl group of 3 with Dess-Martin reagent[4] gave the ketoester (4) (mp 109-110°C) in 98% yield. The carbonyl group of 4 was protected as the thioketal (5) (gummy solid, 81%) as required for the selective reduction of the ester function of it, and for later construction of ring C part. After reduction of 5 with $LiBH_4$ in refluxing THF, addition of NaOMe (1.0 equiv.) facilitated the cyclization of the resulting alcohol intermediate to afford oxazolone (6) (mp 217-220°C) in 80% yield. The final elaboration of the ring C part was achieved by the condensation of 6 with 1.5 equiv. of 3,4,5-trimethoxybenzaldehyde dimethyl acetal in the presence of 2.0 equiv. of trifluoromethanesulfonic acid in trifluoroethanol at room temperature. Aqueous work up and successive purification on column chromatography affforded cyclized product (7) (mp



[a]piperonal, KOH, EtOH. [b]ClCOOEt, K_2CO_3, H_2O. [c]Me_2SO_4, K_2CO_3, acetone. [d]Dess-Martin reagent, CH_2Cl_2. [e]1,3-propanedithiol, $BF_3 \cdot OEt_2$, CH_2Cl_2. [f]$LiBH_4$, THF then NaOMe. [g]3,4,5-trimethoxybenzaldehyde dimethyl acetal, CF_3SO_3H, CF_3CH_2OH.

Scheme 1

193-196°C) in 68% yield. The relative stereochemistry of 7 was confirmed by observation of a positive NOE between H-3 and H-2'. The reductive conversion of 7 to 1 was already reported.[1a,c]

REFERENCES AND NOTES

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2. K. N. F. Shaw and S. W. Fox, J. Am. Chem. Soc., 1953, **75**, 3421.
3. Although spectral data and chromatographic mobilities of 3 suggested its diastereomeric homogeneity, we didn't determine the relative stereochemistry of it.
4. D. B. Dess and J. C. Martin, J. Org. Chem., 1983, **48**, 4155.
5. Spectral data:

   2: ^{1}H-Nmr (300 MHz,DMSO-d_6) δ= 6.94(1H,s), 6.83(2H,s), 5.98(2H,s), 4.97(1H,d,J=4.2 Hz), 3.35(1H,d,J=4.2 Hz).

   3: ^{1}H-Nmr (400 MHz,$CDCl_3$) δ= 6.87(1H,d,J=1.4 Hz), 6.81(1H,dd,J=8.1,1.4 Hz), 6.76(1H,d,J=8.1Hz), 5.94(2H,s), 5.47(1H,br d,J=8 Hz), 5.14(1H,br t,J=3 Hz), 4.50(1H,br d,J=8 Hz), 4.04 (2H,br q,J=7 Hz), 3.75(3H,s), 2.81(1H,br s), 1.19(3H,br t,J=7 Hz). ^{13}C-Nmr (75 MHz,$CDCl_3$) δ= 171.2(s), 156.5(s), 147.6(s), 147.2(s), 133.8(s), 119.3(d), 107.9(d), 106.5(d), 101.0(t), 73.2(d), 61.3(t), 59.9(d), 52.5(q), 14.3(q).

   4: ^{1}H-Nmr (300 MHz,$CDCl_3$) δ= 7.78(1H,dd,J=8.2,1.7 Hz), 7.53(1H,d,J=1.7 Hz), 6.90(1H,d, J=8.2 Hz), 6.07(2H,s), 6.05(1H,br d,J=8.2 Hz), 5.90(1H,d,J=8.2 Hz), 4.15(2H,q,J=7.1Hz), 3.72(3H,s), 1.26(3H,t,J=7.1 Hz). ^{13}C-Nmr (100 MHz,$CDCl_3$) δ= 189.4(s), 167.6(s), 155.9(s), 153.1(s), 148.5(s), 128.8(s), 126.6(d), 108.9(d), 108.2(d), 102.2(t), 61.7(t), 59.1(d), 53.1(q), 14.5(q).

   5: ^{1}H-Nmr (300 MHz,$CDCl_3$) δ= 7.43(1H,d,J=2.0 Hz), 7.40(1H,dd,J=8.3,2.0 Hz), 6.80(1H,d, J=8.3 Hz), 5.99(2H,s), 5.55(1H,br d,J=9.3 Hz), 4.74(1H,d,J=9.3 Hz), 4.11(2H,q,J=7.1 Hz), 3.56(3H,s), 2.80-2.67(4H,m), 1.96-1.87(2H,m), 1.26(3H, t,J=7.1 Hz). ^{13}C-Nmr (75 MHz,

$CDCl_3$) δ= 168.8(s), 155.7(s), 148.1(s), 147.2(s), 131.3(s), 123.4(d), 109.6(d), 107.8(d), 101.4(t), 62.4(d), 61.4(t), 61.1(s), 52.0(q), 27.4(t), 27.3(t), 24.2(t), 14.4(q).

6: ^{1}H-Nmr (400 MHz,DMSO-d_6) δ= 8.01(1H,br s), 7.34-7.32(2H,m), 6.95(1H,d,J=8.7Hz), 6.06(1H,s), 6.05(1H,s), 4.29-4.17(3H,m), 2.93-2.80(3H,m), 2.66-2.48(2H,m), 1.94-1.71 (2H,m). ^{13}C-Nmr (100 MHz,DMSO-d_6) δ= 158.1(s), 147.5(s), 146.7(s), 130.9(s), 123.0(d), 109.2(d), 107.8(d), 101.3(t), 64.9(t), 61.1(s), 60.0(d), 26.0(t)x2, 24.1(t).

7: ^{1}H-Nmr (400 MHz,$CDCl_3$) δ= 7.55(1H,s), 6.68(1H,s), 6.39(2H,s), 6.14(1H,s), 6.11(1H,d, J=1.1 Hz), 6.09(1H,d,J=1.1 Hz), 4.65(1H,dd,J=9.0,4.8 Hz), 4.53(1H,dd,J=9.5,9.0 Hz), 4.30 (1H,dd,J=9.5,4.8 Hz), 3.83(3H,s), 3.77(6H,s). ^{13}C-Nmr (100 MHz,$CDCl_3$) δ= 190.7(s), 156.6 (s), 153.7(s), 153.5(s), 148.6(s), 138.7(s), 138.3(s), 133.6(s), 125.0(s), 107.6(d), 106.2(d), 105.9(d), 102.5(t), 64.8(t), 60.8(q), 56.5(d), 56.4(q), 55.6(d).

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