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The synthesis of (*S*)-(+)-pantolactone and its analogues from an ephedrine-derived morpholinone

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Dedicated to Dr. S. Rajappa on his 70th birthday

Abstract—An efficient general route for the enantioselective synthesis of (*S*)-(+)-pantolactone and its analogues has been developed from an ephedrine-derived chiral morpholin-3-one. Selective dialkylation of an ephedrine-derived chiral template without epimerization is the key step in this synthesis.

The asymmetric synthesis of pantolactone and its analogues continues to be an area of active interest to organic chemists as a consequence of their biological activity, utility as a secondary alcohol derived chiral auxiliary[1] and as a building block in the synthesis of natural products.[2] The taurine derivative of pantothenic acid (pantoyl taurine) has been shown[3] to inhibit the growth of streptococci, pneumococci, plasmodium relictum[4] and certain strains of diptheria bacilli.[5] Furthermore, pantolactone is an important starting compound for pantothenic acid[6] (a member of B complex vitamins), calcium pantothenate[7] (enzyme cofactor vitamin), (*R*)-panthenol[8] (bactericide) and (*R*)-pantetheine[9] (growth factor). Enantiomerically pure pantolactone and its analogues have been obtained by chemical[10] and enzymatic resolution of the racemate,[11] enantioselective reduction of 3,3-dimethyl-2-oxobutyrolactone,[12] Sharpless asymmetric dihydroxylation of the corresponding cyclic silylketene acetal, a pantolactone precursor,[13] asymmetric functionalization of linear or cyclic precursors[14] and asymmetric aldol reaction of silyl enolate with ethyl glyoxylate.[15]

As a part of our ongoing research programme on the application of commercially available ephedrine as a chiral template for asymmetric synthesis,[16] we herein report the efficient use of ephedrine for the enantioselective synthesis of pantolactone and its analogues. Recently, the synthesis of pantolactone has been achieved in our laboratory by a stereoselective Prins reaction on an ephedrine-derived chiral alkylidine morpholinone.[17] However, this synthesis not only gives a low overall yield of pantolactone but also has limitations in it being utilized as a general route for the synthesis of analogues. We envisaged, α,α-dialkylation of ephedrine-derived chiral morpholin-3-one ester **4** as a key strategy, which on further functional group transformations would give us pantolactone and its various analogues. While there have been numerous reports on the asymmetric synthesis of pantolactone derivatives, to the best of our knowledge, there has been no report on a dialkylation strategy for the introduction of the *gem*-dialkyl moiety in pantolactone or its analogues.

The starting morpholin-3-one ester **4** was easily accessible in its enantiomerically pure form commercially available ephedrine in three steps following our previously reported procedure[16b] in good overall yield (Scheme 1). Introduction of the *gem*-dialkyl moiety, a key step in the synthesis, via selective dialkylation on the α-carbon to the ester carbonyl was then investigated. Different bases such as LDA, NaH, KO^{t}Bu and KH were employed for the dialkylation of ester **4** using methyl iodide as an alkylating agent. The reaction did not work with NaH and gave back the starting material, while LDA gave an inseparable complex mixture of products. However, dimethylated product **5a** could be

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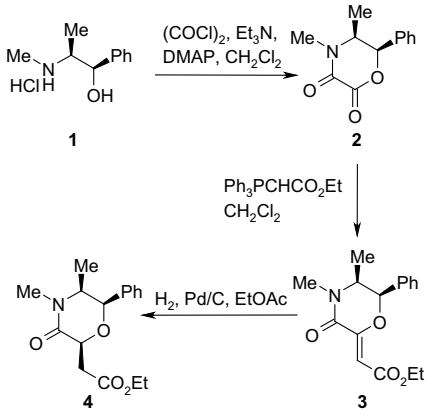
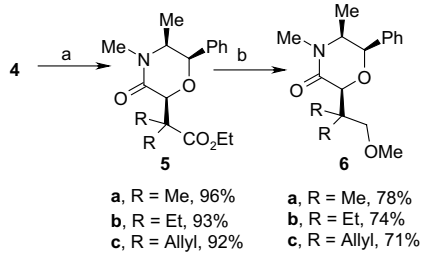


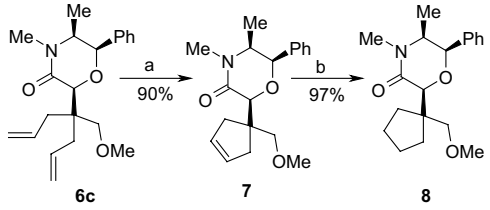
Scheme 1.

obtained for the first time in moderate yield (65%) using KO^{t}Bu and methyl iodide using THF as a solvent. Further studies on dimethylation showed that the base of choice was KH, which gave the dimethylated product **5a** in 96% yield.[18] No epimerization of the product was observed (^{1}H NMR) under these reaction conditions. Other dialkylated products **5b–c** were also obtained in excellent yields (92–93%) using the corresponding alkyl halides and KH (Scheme 2).



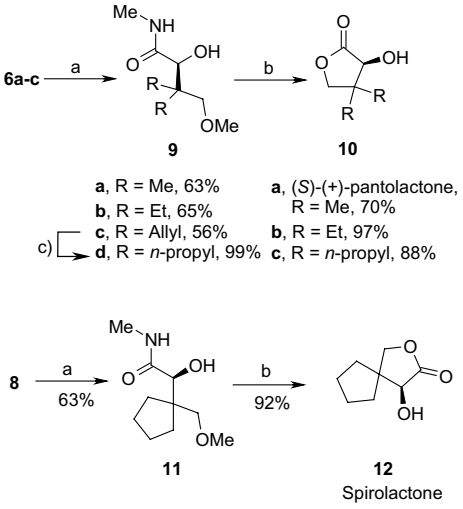
Scheme 2. Reagents and conditions: (a) KH, R–X, THF, 0 °C to rt; (b) (i) DIBAL-H, THF, −78 °C to rt, (ii) NaH, MeI, THF.

Further selective reduction of the dialkylated esters **5a–c** was achieved by excess DIBAL-H to give the corresponding alcohols, which were protected as methyl ethers **6a–c** (Scheme 2) in 71–78% overall yields.[19] Other protecting groups, such as acetate, caused complications during the removal of the chiral auxiliary, while ethoxyethyl and methoxymethyl gave poor yields. Diallyl compound **6c** offers an added advantage, as manipulation of the double bonds is possible. One such conversion of **6c** to five-membered cyclic alkene **7** was achieved by ring closing metathesis (RCM) using Grubb's catalyst. The RCM product **7** was hydrogenated using a Pd/C catalyst to give cyclopentyl compound **8** (Scheme 3). The morpholinones **6a–c** and **8** are protected versions of the required α,γ-dihydroxy butyric acid, a precursor to pantolactone and its analogues. The ephedrine portion in **6a–c** and **8** was removed by reduction with Na/NH_3,[20] which gave the α-hydroxy-γ-methoxy butyramides **9a–c**



Scheme 3. Reagents and conditions: (a) Grubb's catalyst, CH_2Cl_2, rt; (b) H_2, Pd/C, EtOAc.

and **11** (Scheme 4). Conversion of the hydroxy butyramides to the target lactones was achieved by a one-pot reaction sequence. The primary hydroxyl group in butyramides was liberated by demethylation with BBr_3 in methylene chloride at −78 °C. Subsequent acid catalyzed lactonization at −15 °C, which presumably involves a very facile intramolecular acyl transfer from N to O, furnished (*S*)-(+)-pantolactone **10a**[21] and its analogues **10b–c** and **12** in 70–97% yields (Table 1) with high enantiomeric excesses.[22]

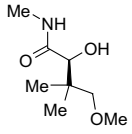
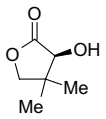
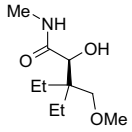
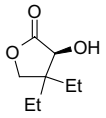
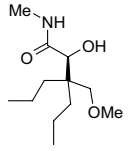
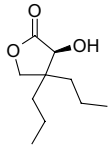
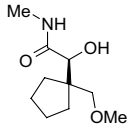
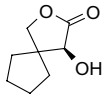


Scheme 4. Reagents and conditions: (a) (i) Na/liq. NH_3, THF, −78 °C, (ii) MeOH; (b) (i) BBr_3, CH_2Cl_2, −78 to −15 °C, (ii) H_2O, −15 °C, (iii) H_2SO_4, −15 °C to rt; (c) H_2, Pd/C, EtOAc.

The simplicity of the above synthetic sequence makes it viable for the synthesis of pantolactone and its analogues on a preparative scale. In this regard it is noteworthy that several grams of the key intermediate **6a–c** and **8** can be prepared readily.

In conclusion, a general route for the enantioselective synthesis of (*S*)-(+)-pantolactone and its analogues has been developed from an ephedrine-derived chiral morpholinone. The above method should provide access to a variety of enantiomerically enriched β,β-dialkyl-α-hydroxy-γ-butyrolactones in either enantiomeric forms, since both enantiomers of ephedrine are commercially available.

Table 1. Synthesis of pantolactone and its analogues **10a–c** and **12**

Substrate		Product		Yield[a] (%)	$[\alpha]_D^{25}$ (Solvent)	Ee[b] (%)
	**9a**		**10a**	70	+51.8 (H_2O)	91
	**9b**		**10b**	97	+14.9 (MeOH)	91
	**9d**		**10c**	88	+8.4 ($CHCl_3$)	92
	**11**		**12**	92	+18.6 ($CHCl_3$)	94

[a] Isolated yields.
[b] Enantiomeric excess of the lactones was determined by chiral GC analysis on a CP-Chiracel-Dex CB column.

Acknowledgements

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References and notes

1. (a) O'Meara, J. A.; Gardee, N.; Jung, M.; Ben, R. N.; Durst, T. J. *J. Org. Chem.* **1998**, *63*, 3117; (b) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641, and references cited therein; (c) Hansen, M. M.; Bertsch, C. F.; Harkness, A. R.; Huff, B. E.; Hutchison, D. R.; Khau, V. V.; LeTourneau, M. E.; Martinelli, M. J.; Misner, J. W.; Peterson, B. C.; Rieck, J. A.; Sullivan, K. A.; Wright, I. G. *J. Org. Chem.* **1998**, *63*, 775.
2. (a) Kagan, F.; Heinzelman, R. V.; Weisblat, D. I.; Greiner, W. *J. Am. Chem. Soc.* **1957**, *79*, 3545; (b) Neidlein, R.; Greulich, P. *Helv. Chim. Acta* **1992**, *75*, 2545; (c) Fischer, G. C.; Turakhia, R. H.; Morrow, C. J. *J. Org. Chem.* **1985**, *50*, 2011; (d) Dolle, R. E.; Nicolou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691; (e) Lavallee, P.; Ruel, R.; Greiner, L.; Bissonnette, M. *Tetrahedron Lett.* **1986**, *27*, 679; (f) Sone, H.; Suenaga, K.; Bessho, Y.; Kondo, T.; Kigoshi, H.; Yamada, K. *Chem. Lett.* **1998**, 85.
3. Kuhn, R.; Wieland, T.; Moller, E. F. *Ber.* **1941**, *74*, 1605.
4. Winterbottom, R.; Clapp, J. W.; Miller, W. H.; English, J. P.; Roblin, R. O., Jr. *J. Am. Chem. Soc.* **1947**, *69*, 1393.
5. Roblin, R. O., Jr. *Chem. Rev.* **1946**, *38*, 255.
6. (a) Lehninger, A. L. *Principles of Biochemistry*; Worth Publishers: New York, 1987, pp 256–257; (b) Brown, G. M.; Williamson, M. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1982**, *53*, 345.
7. Lipmann, F. *Science* **1954**, *120*, 855.
8. Shimizu, S.; Tani, Y.; Ogata, K. *Agric. Biol. Chem.* **1974**, *38*, 1989.
9. King, T. E.; Stewart, C. J.; Cheldelin, V. H. *J. Am. Chem. Soc.* **1953**, *75*, 1290.
10. (a) Stiller, E. T.; Harris, S. A.; Finkelstein, J.; Keresztesy, J. C.; Folkers, K. *J. Am. Chem. Soc.* **1940**, *62*, 1785; (b) Fuji, K.; Node, M.; Murata, M.; Terada, S.; Hashimoto, K. *Tetrahedron Lett.* **1986**, *27*, 5381; (c) Bevinakatti, H. S.; Banerji, A. A.; Newadkar, R. V. *J. Org. Chem.* **1989**, *54*, 2453; (d) Kagan, F.; Heinzelman, R. V.; Weisblat, D. I.; Greiner, W. *J. Am. Chem. Soc.* **1957**, *79*, 3545.
11. Baumann, M.; Hauer, B. H.; Bornscheuer, U. T. *Tetrahedron: Asymmetry* **2000**, *11*, 4781.
12. (a) Ojima, I.; Kogure, T.; Terasaki, T.; Achiwa, K. *J. Org. Chem.* **1978**, *43*, 3444; (b) Kagan, H. B.; Tahar, M.; Fiaud, J.-C. *Tetrahedron Lett.* **1991**, *32*, 5959; (c) Genet, J.-P.; Pinel, C.; Mallart, S.; Juge, S.; Cailhol, H.; Laffittee, J. A. *Tetrahedron Lett.* **1992**, *33*, 5343; (d) Takahashi, H.; Hattori, M.; Chiba, M.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1986**, *27*, 4477; (e) Roucoux, A.; Agbossou, F.; Mortreux, A.; Petit, F. *Tetrahedron: Asymmetry* **1993**, *4*, 2279; (f) Chiba, M.; Takahashi, H.; Takahashi, H.; Morimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1987**, *28*, 3675.
13. Upadhya, T. T.; Gurunath, S.; Sudalai, A. *Tetrahedron: Asymmetry* **1999**, *10*, 2899.
14. (a) Rao, A. V. R.; Rao, S. M.; Sharma, G. V. M. *Tetrahedron Lett.* **1994**, *35*, 5735; (b) Effenberger, F.; Eichhorn, J.; Roos, J. *Tetrahedron: Asymmetry* **1995**, *6*, 271.
15. Evans, D. A.; Wu, J.; Masse, C. E.; MacMillan, D. W. C. *Org. Lett.* **2002**, *4*, 3379.
16. (a) Shinkre, B. A.; Puranik, V. G.; Bhawal, B. M.; Deshmukh, A. R. A. S. *Tetrahedron: Asymmetry* **2003**, *14*,

453; (b) Pansare, S. V.; Shinkre, B. A.; Bhattacharyya, A. *Tetrahedron* **2002**, *58*, 8985.
17. (a) Pansare, S. V.; Bhattacharyya, A. *Tetrahedron* **2003**, *59*, 3275; (b) Pansare, S. V.; Jain, R. P. *Org. Lett.* **2000**, *2*, 175.
18. Typical procedure for dialkylation of morpholinone ester **4**: To a stirred suspension of KH (712 mg, 17.7 mmol) in anhydrous THF (10 mL) at 0 °C was added a solution of morpholinone ester **4** (1.475 g, 5.07 mmol) in anhydrous THF (20 mL) dropwise over a period of 45 min. After stirring for 1 h at 0 °C, methyl iodide (1.42 mL, 22.8 mmol) was added dropwise and the reaction mixture allowed to warm up to room temperature and stirred for 12 h. Saturated NH_4Cl solution (~2 mL) was then added and the solvent removed under reduced pressure. The precipitated solid was dissolved in the minimum amount of water (~3 mL) and extracted with ethyl acetate (3×15 mL). The combined extracts were washed with brine solution (10 mL), dried over Na_2SO_4 and concentrated to furnish a crude product, which was purified by flash column chromatography on silica gel using ethyl acetate/petroleum ether (1:1) to give **5a** as a clear colourless gum (1.55 g, 96%). $[\alpha]_D^{25} = -131.5$ (*c* 1.17, $CHCl_3$); IR ($CHCl_3$): 1649, 1728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (d, 3H, $J = 6.8$ Hz, CH_3CH), 1.28 (t, 3H, $J = 7.1$ Hz, CH_3CH_2), 1.32 (s, 3H, CH_3C), 1.41 (s, 3H, CH_3C), 3.01 (s, 3H, NCH_3), 3.49–3.55 (dq, 1H, $J = 2.8$, 6.8 Hz, $CHCH_3$), 4.15–4.28 (m, 2H, OCH_2), 4.68 (s, 1H, CHCO), 5.04 (d, 1H, $J = 2.8$ Hz, PhCH), 7.22–7.42 (m, 5H, ArH); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 13.0, 13.9, 19.1, 23.2, 33.1, 45.9, 58.3, 60.4, 76.3, 81.8, 125.1, 127.4, 128.2, 137.6, 167.4, 175.4; MS (*m*/*z*): 319 (M^+); Anal. Calcd for $C_{18}H_{25}NO_4$: C 67.69, H 7.89, N 4.39, obtained: C 67.80, H 8.17, N 4.22.
19. Data for **6a**: A clear colourless gum. $[\alpha]_D^{25} = -191.7$ (*c* 3.6, $CHCl_3$); IR ($CHCl_3$): 1649 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.86 (d, 3H, $J = 6.4$ Hz, CH_3CH), 1.06 (s, 6H, $(CH_3C)_2$), 2.91 (s, 3H, NCH_3), 3.25 (s, 3H, OCH_3), 3.34 (d, 1H, $J = 8.7$ Hz, OCH_2), 3.36–3.42 (dq, 1H, $J = 2.8$, 6.4 Hz, $CHCH_3$), 3.46 (d, 1H, $J = 8.7$ Hz, CH_2O), 4.13 (s, 1H, CHCO), 4.83 (d, 1H, $J = 2.8$ Hz, PhCH), 7.15–7.30 (m, 5H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.7, 21.7, 33.0, 39.8, 58.4, 58.7, 76.0, 79.4, 81.3, 125.1, 127.1, 127.9, 138.0, 168.3; MS (*m*/*z*): 291 (M^+); Anal. Calcd for $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81, obtained: C 70.30, H 8.85, N 5.05.
20. Typical procedure for the removal of ephedrine portion: To anhydrous liquid ammonia (10 mL), was added Na (329 mg, 14.3 mmol) at −78 °C and the mixture stirred for 15 min. To the resulting blue solution was added a solution of morpholinone **6a** (250 mg, 1.43 mmol) in THF (1.5 mL). The mixture was stirred at −78 °C (3 min), methanol (5 mL) was then added and the mixture stirred further at room temperature until ammonia was completely removed. The solvent was removed under reduced pressure and the residue partitioned with ethyl acetate (10 mL) and water (2 mL). The ethyl acetate layer was separated and the aqueous layer extracted three times with ethyl acetate. The combined extracts were washed with brine solution (5 mL), dried over Na_2SO_4 and concentrated to obtain a crude product, which upon purification by flash column chromatography (2:3 EtOAc/Pet-ether) furnished **9a** as a colourless gum (95 mg, 63%). IR ($CHCl_3$): 1666, 3431 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.0 (s, 6H, $C(CH_3)_2$), 2.85 (d, 3H, $J = 5.1$ Hz, NCH_3), 3.25 (d, 1H, $J = 9.2$ Hz, CH_2), 3.35 (d, 1H, $J = 9.2$ Hz, CH_2), 3.35 (s, 3H, OCH_3), 4.00 (d, 1H, $J = 3.6$ Hz, CH), 4.45 (d, 1H, $J = 3.6$ Hz, OH), 6.80 (br s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$): δ 20.2, 21.6, 25.3, 38.4, 59.1, 77.9, 81.7, 172.9; MS (*m*/*z*): 175 (M^+); Anal. Calcd for $C_8H_{17}NO_3$: C 54.84, H 9.78, N 7.99, obtained: C 54.99, H 9.97, N 8.23.
21. Typical procedure for lactonization: To a stirred solution of **9a** (120 mg, 0.92 mmol) in anhydrous dichloromethane (7 mL) was added at −78 °C boron tribromide (1 M solution in dichloromethane 9.2 mL, 9.2 mmol) with the resulting reaction mixture gradually warmed to −15 °C with continuous stirring. The reaction was kept at −15 °C for 2 h with water (3.5 mL) then added over a period of 5 min. The mixture was stirred for a further 15 min after which 6 M H_2SO_4 (3.5 mL) was added. The mixture was stirred overnight, during which time it was warmed to ambient temperature. The mixture was then cooled in an ice bath and neutralized via the addition of small portions of solid sodium bicarbonate. The resulting semi-solid residue was then extracted with dichloromethane (3×15 mL). The combined dichloromethane extracts were dried over Na_2SO_4 and concentrated to obtain crude lactone, which was purified by flash column chromatography to furnish **10a** as a white solid (62 mg, 70%). $[\alpha]_D^{25} = +51.8$ (*c* 2, H_2O); IR (H_2O): 1782, 3446 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 1.11 (s, 3H, CH_3C), 1.26 (s, 3H, CH_3C), 2.34 (bs, 1H, OH), 3.97 (d, 1H, $J = 9.1$ Hz, OCH_2), 4.05 (d, 1H, $J = 9.1$ Hz, CH_2O), 4.14 (s, 1H, CHCO); ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 18.8, 22.9, 40.9, 75.8, 76.3, 177.3; MS (*m*/*z*): 130 (M^+); Anal. Calcd for $C_6H_{10}O_3$: C 55.37, H 7.74, Found: C 55.65, H 7.96. Enantiomeric excess of **10a** was 91% by GC analysis.
22. Enantiomeric excess of the lactones **10a–c** and **12** was determined by GC analysis on a CP-Chiracel-Dex CB capillary column (25.0 m×250 μm×0.25 μm). Temperature gradient: 60 °C (2 min); 3 °C min^{-1} to 120 °C (3 min); 20 °C min^{-1} to 180 °C (10 min); carrier gas: nitrogen; flow rate: 2 mL min^{-1}.