

Bicyclic Lactams derived from Serine or Cysteine and 2-Methylpropanal

Halima Bagum,[†] Bethany R. Shire,[†] Kirsten E. Christensen,[†] Miroslav Genov,[‡] Alexander Pretsch,[‡] Dagmar Pretsch,[‡] and Mark G. Moloney^{*,†,‡,‡}

[†]The Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford. OX1 3TA

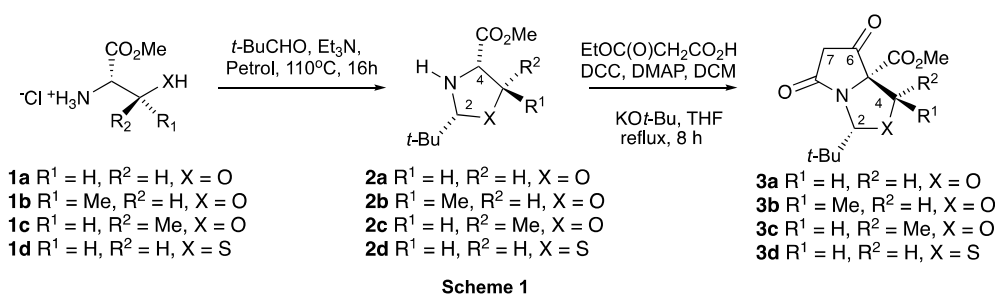
[#]Oxford Suzhou Centre for Advanced Research, Building A, 388 Ruo Shui Road, Suzhou Industrial Park, Jiangsu, 215123, P.R. China.

[‡]Oxford Antibiotic Group, The Oxford Science Park, Magdalen Centre, Oxford OX4 4GA, UK.

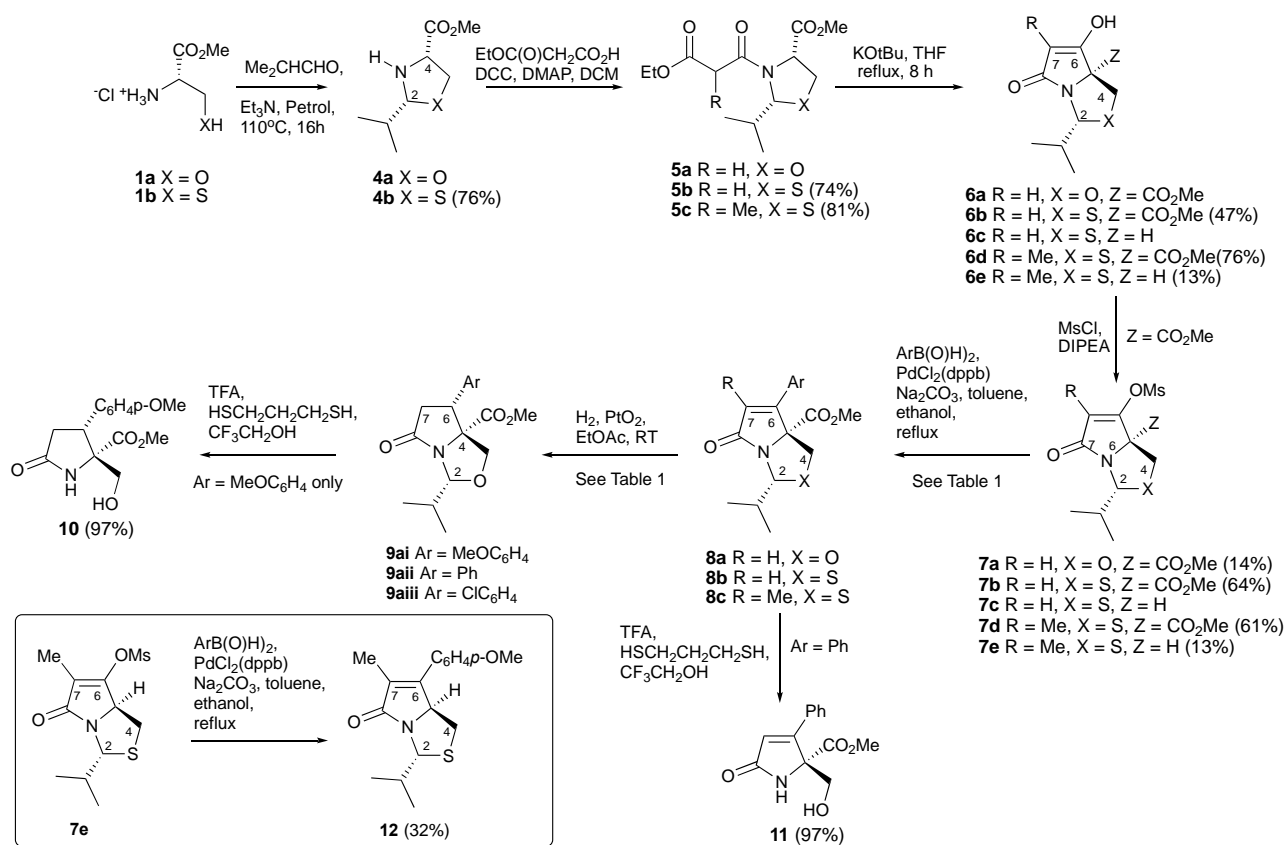
mark.moloney@chem.ox.ac.uk

Abstract: Bicyclic lactams may be prepared from serine or cysteine and 2-methylpropanal; the resulting *S,N*- heterocycles are more stable than the *O,N*- heterocycles but both are synthetic intermediates capable of further elaboration.

We have shown that L-serine, L-cysteine, L-allothreonine and L-threonine methyl esters **1a-d** may be converted to their corresponding *O,N*- or *S,N*-heterocycles **2a-d** by reaction with pivaldehyde, and that these in turn may be converted to tetramates **3a-d** by a highly chemo- and enantioselective Dieckmann cyclisation using the literature protocols.^{1, 2, 3} The *t*-butyl group acts simultaneously as a protecting and chemoselective directing group, principally from its bulk. One disadvantage of this process is the expense and availability of pivaldehyde, and the question arose whether 2-methylpropanal might provide an alternative. Although the use of other aldehydes and especially benzaldehydes has been shown for cysteine,⁴ where the *S,N*-heterocycles are more stable,^{5, 6} the possibility of similar variation for the *O,N*-heterocycle system was less certain. The feasibility of preparing and using such tetramates have been investigated and is reported here.



Methyl ester hydrochlorides of the amino acids L-serine and L-cysteine **1a** and **1d** were treated with 2-methylpropanal/triethylamine following Seebach's protocol (Scheme 1)⁷ to furnish oxazolidine **4a** and thiazolidine **4b** as mixtures of diastereomers which were used directly without purification; the preference of the latter for *cis*-2,5 diastereomer results from ring-chain tautomerism giving the more stable isomer.^{5, 8, 9} DCC coupling gave malonamides **5a,b** and subsequent Dieckmann cyclization afforded the novel methyl ester tetramates **6a** (14%) or **6b** (47%);¹⁰ the relative stereochemistry of key intermediates was established NOE analysis (Figure 1). It is evident that the isopropyl group is capable of directing a similar chemical outcome to that of the *t*-butyl group,^{8, 11} although this comes with complication in the NMR spectrum as a result of the non-symmetrical nature of the isopropyl system. In the case of the thiazolidine system, bicyclic tetramate **6b** was obtained along with decarboxylated **6c** as an inseparable mixture. Tetramates **6a,b** were readily converted to mesylates **7a,b** in 14 and 64% yield;¹⁰ the significantly better yields in the case of the latter again reflect the better stability to acid (and therefore chromatography) of the *S,N*- system over the *O,N*- one. For the oxazolidine system, difficulties with purification, thought to arise from the greater acid sensitivity of this system, meant that crude material needed to be taken on until formation of the mesylate **7a**, which could readily be isolated in pure form. With mesylates **7a,b** in hand, Suzuki coupling with 1.5 eq of aryl boronic acid resulted pyrrolinone derivatives **8ai-iii** and **8bi-iii** (Table 1).¹⁰ The structures of **8aii** and **8bii** were further confirmed by single crystal x-ray analysis (Figure 2).¹²



Scheme 2

Table 1: Suzuki coupling of **7a,b** with arylboronic acids and hydrogenation of **8ai-aiii**.

Compound	Ar	Reaction time (h)	Product	Yield (%)	Reaction time (h)	Product	Yield (%)
7a	4-MeOC ₆ H ₄	6	8ai	47	6	9ai	82
	C ₆ H ₅	6	8aii	45	5	9aii	75
	4-ClC ₆ H ₄	3	8aiii	40	6	9aiii	85
7b	4-MeOC ₆ H ₄	3	8bi	72	-	-	-
	C ₆ H ₅	3	8bii	74	-	-	-
	4-ClC ₆ H ₄	5	8biii	41	-	-	-
7c	4-MeOC ₆ H ₄	24h	8ci	13	-	-	-
	C ₆ H ₅	20h	8cii	12	-	-	-
	4-ClC ₆ H ₄	24h	8ciii	11	-	-	-

^a 4-chlorophenylboronic acid: 1.05 eq

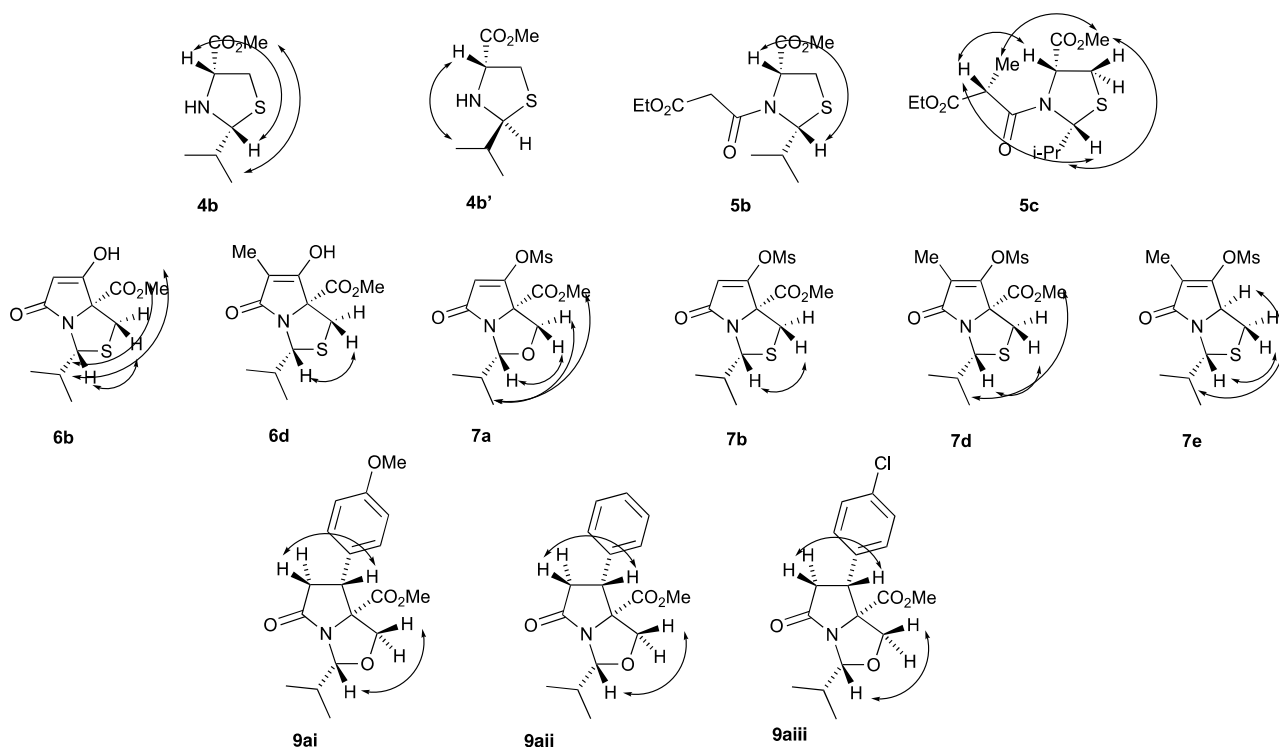


Figure 1

Figure 1: NOE Analysis of selected compounds.

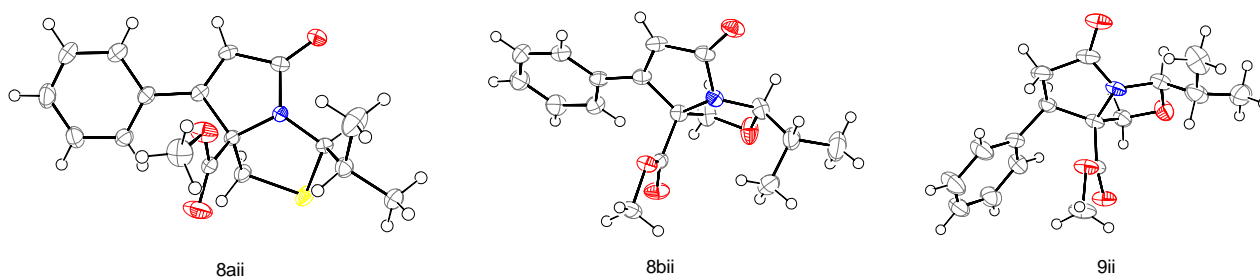


Figure 2: Single crystal X-Ray crystal structure of **8aii**, **8bii**, **9aii**.¹² Displacement ellipsoids are drawn at 50% probability.

Treatment of pyrrolinones **8ai-iii** with H_2/PtO_2 furnished acid derivatives **9ai-iii** in high yields (Table 1), and of interest was that the isolation of these products by *flash* column chromatography was straightforward. Their stereochemistry was assigned by NOE analysis, all of showing strong NOE between *endo*-H4-H2 and *endo*-H7-H6 (Figure 1) and further confirmed by the X-ray crystal structure of **9aii** (Figure 2).¹² Representative compounds **8aii** and **9ai** were subjected to *N,O*-acetal deprotection using Corey-Reichard protocol¹³ and gave the pyroglutaminols **10** and **11** in excellent

yield (Scheme 2). The easier deprotection of the isopropyl system over the *t*-butyl one is noteworthy, and again reflects their increased acid lability.¹

This approach could also be extended by *N*-acylation of thiazolidine **4b** with ethyl α -methylmalonyl chloride and pyridine to furnish *cis*-2,5 malonamide **5c** (Scheme), found as a mixture of C7 epimers with 7*R* as a major one (NOE, Figure 1) and 1D gradient NMR spectroscopy showed the presence of rotameric exchange. Dieckmann cyclisation under basic conditions resulted in inseparable C7-methyl tetramates **6d** and **6e**.¹⁰ The stereochemistry of the major tetramic acid **6d** was determined by NOE analysis (Figure 1). The treatment of this mixture with MsCl/DIPEA gave mesylates **7d** and **7e** in 61% and 13% isolated yield, respectively.¹⁰ The stereochemistry of both mesylates **7d** and **7e** were confirmed by NOE analysis (Figure 1), and Suzuki coupling with arylboronic acids furnished the desired coupling adducts **8ci-iii** and **12** (Scheme 1 and Table 2).¹⁰ However, the reaction was much slower in this case and probably reflects the greater steric bulk in this system.

Broth assay of some of these compounds (**8ai-aiii**, **8bi-biii**, **8ci-8ciii** and **13**) against Gram positive (Methicillin resistant *Staphylococcus aureus*) and Gram negative (*Escherichia coli* (EC 34) bacteria showed no activity, confirming earlier results seen with related pyroglutamate derivatives.¹⁴

Conclusion

We have shown that bicyclic lactams may be prepared from serine or cysteine and 2-methylpropanal; the resulting *S,N*- heterocycles are more stable than the *O,N*- heterocycles but both are synthetic intermediates capable of further elaboration. This approach neatly complements earlier work leading to C-6 and C-7 functionalisation in related bicyclic systems.¹⁵

Acknowledgements

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References

Dieckmann Cyclisation:³ To a solution of *N*-acyl oxazolidine or thiazolidine **5a,b** (1.0 eq) in anhydrous THF was added potassium *tert*-butoxide (1.05 eq). The mixture was heated at reflux for 3 h. The reaction mixture was separated between Et₂O and water, the aqueous phase was acidified with 2 M aqueous HCl and extracted with EtOAc. The organic layer was washed with a 1 M aqueous solution of NaH₂PO₄ and brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the methyl ester tetramic acids **6a-e**.

Synthesis of Mesylate:¹⁶ Tetramic acid **6a-e** (1.0 eq) was dissolved in DCM under nitrogen atmosphere. Methanesulfonyl chloride (1 eq) and DIPEA (2 eq) were added to this solution. The resulting mixture was stirred for 2-6 h at room temperature until total consumption of the starting material. The reaction mixture was washed with 5% HCl, 5% NaHCO₃, and brine, dried over MgSO₄, and filtered. The solvent was removed *in vacuo*, and the residue was chromatographed on silica gel using ethyl acetate:petroleum ether as eluants to give mesylates **7a,c**.

Representative reaction: Tetramic acids (**6d** + **6e**, 2.32 g, 8.55 mmol) was reacted with MsCl (0.66 mL, 8.55 mmol) and DIPEA (2.9 mL, 17.1 mmol) in DCM (85 mL). Purification by flash column chromatography (20-30% EtOAc in petroleum ether) furnished isolated mesylates **7d** and **7e**. Yield 61% (1.82 g); colourless oil; R_f (40% EtOAc in Petrol) 0.37; $[\alpha]_D^{25} +235.0$ (*c* 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2960 (C-H), 2935 (C-H), 1747 (C=O), 1713 (C=O); δ_{H} (400 MHz, CDCl₃): 0.87 (3H, d, *J* 6.6, CH(CH₃)), 1.02 (3H, d, *J* 6.6, CH(CH₃)), 1.78-1.84 (1H, m, CH(CH₃)₂), 1.85 (3H, s, C(7)CH₃), 2.84 (1H, d, *J* 11.1, C(4)H_AH_B), 3.23 (3H, s, OSO₂CH₃), 3.58 (1H, d, *J* 11.1, C(4)H_AH_B), 3.76 (3H, s, CO₂CH₃), 4.70 (1H, s, *J* 9.7, C(2)H); δ_{C} (100 MHz, CDCl₃): 8.6 (C(7)CH₃), 19.6, 20.2 (CH(CH₃)₂), 35.2 (C(4)), 36.9 (CH(CH₃)₂), 39.5 (OSO₂CH₃), 53.7 (CO₂CH₃), 66.8 (C(2)), 78.2 (C(5)), 124.0 (C(7)), 154.0 (CO₂CH₃), 168.4 (C(8)), 171.4 (C(6)); *m/z* ([ESI]⁺) 372.0 ([M+Na]⁺, 100%); HRMS ([ESI]⁺) found 372.0547, C₁₃H₁₉NNaO₆S₂ ([M+Na]⁺) requires 372.0546.

Suzuki Coupling:¹⁷ A mixture of 1,4-bis(diphenylphosphino)butane (0.06 eq) and bis(benzonitrile)palladium(II) chloride (0.05 eq) in dry toluene was stirred at room temperature under nitrogen atmosphere for 30 minutes to form a creamy orange slurry of [1,4-bis(diphenylphosphino)butane] palladium(II) chloride. Mesylate (1.0 eq), boronic acid (1.05-1.8 eq), ethanol (7.0 eq), 1M aqueous sodium carbonate solution (9-18 eq) and dry toluene were added to the catalyst and the mixture was refluxed for 3-30 hours. After cooling, water was added, and the mixture was diluted with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried and evaporated *in vacuo* to find the crude product, which was then purified by *flash* column chromatography.

Representative reaction: Mesylate **7a** (210 mg, 0.66 mmol) was reacted with 4-methoxyphenylboronic acid (150 mg, 0.98 mmol), PdCl₂(dppb), 1 M aqueous Na₂CO₃ solution (0.62 mL, 5.94 mmol) in ethanol (0.27 mL, 4.62 mmol) and toluene (12 mL) for 6 h. PdCl₂(dppb) was prepared from (C₆H₅)₂P(CH₂)₄P(C₆H₅)₂ (16.9 mg, 0.04 mmol) and (C₆H₅CN)₂PdCl₂ (12.6 mg, 0.022 mmol) in toluene (2 mL). Yield 47% (102 mg); yellow solid, m. p. 90-92°C; R_f (30% EtOAc in Petrol) 0.25; [α]_D²⁵ +138.9 (c 1.0 in DCM); $\nu_{\max}/\text{cm}^{-1}$ 2954 (C-H), 2868 (C-H), 1743 (C=O), 1712 (C=O); δ_{H} (400 MHz, CDCl₃): 0.91 (6H, dd, *J* 8.9, 6.8, HC(CH₃)₂), 1.80 (1H, dq, *J* 6.8, 5.6, (HC(CH₃)₂), 3.48 (1H, d, *J* 8.3, C(4)H_AH_B), 3.59 (3H, s, CO₂CH₃), 3.77 (3H, s, OCH₃), 4.84 (1H, d, *J* 5.6, C(2)H), 5.02 (1H, d, *J* 8.3, C(4)H_AH_B), 6.19 (1H, s, C(7)H), 6.86 (2H, d, *J* 8.9, C(3')H), 7.31 (2H, d, *J* 8.9, C(2')H); δ_{C} (100 MHz, CDCl₃): 17.1, 17.1 (HC(CH₃)₂), 33.2 (HC(CH₃)₂), 53.3 (CO₂CH₃), 55.5 (OCH₃), 70.3 (C(4)), 76.8 (C(5)), 93.5 (C(2)), 114.7 (C(3')), 119.0 (C(7)), 122.5 (C(1')), 128.8 (C(2')), 159.3 (C(6)), 161.9 (C(4')), 170.1 (CO₂CH₃), 177.5 (C(8)); m/z ([ESI]⁺) 332.1 ([M+H]⁺, 30%); HRMS ([ESI]⁺) found 332.1493, C₁₈H₂₂NO₅ ([M+H]⁺) requires 332.1493.

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1. Bagum, H.; Christensen, K. E.; Genov, M.; Pretsch, A.; Pretsch, D.; Moloney, M. G. *J. Org. Chem.* **2019**, 84, 10257-10279.
2. Bagum, H.; Christensen, K. E.; Pretsch, A.; Genov, M.; Pretsch, D.; Moloney, M. G. *Tetrahedron* **2019**, 75, 130561-130583; Josa-Cullere, L.; Moloney, M. G.; Thompson, A. L. *Synlett* **2016**, 27, (11), 1677-1681.
3. Andrews, M. D.; Brewster, A. G.; Crapnell, K. M.; Ibbett, A. J.; Jones, T.; Moloney, M. G.; Prout, K.; Watkin, D. J. *Chem. Soc., Perkin Trans. 1* **1998**, (2), 223-235.
4. Panduwawala, T. D.; Iqbal, S.; Tirfoin, R.; Moloney, M. G. *Org. Biomol. Chem.* **2016**, 14, 4464-4478; Panduwawala, T. D.; Josa-Cullere, L.; Kuprov, I.; Odell, B.; Moloney, M. G.; Claridge, T. D. W. *J. Org. Chem.* **2016**, 81, (10), 4142-4148.
5. Lazar, L.; Fulop, F. *Eur. J. Org. Chem.* **2003**, (16), 3025-3042.
6. Lazar, L.; Goblyos, A.; Martinek, T. A.; Fulop, F. *J. Org. Chem.* **2002**, 67, (14), 4734-4741; Fulop, F.; Mattinen, J.; Pihlaja, K. *Tetrahedron* **1990**, 46, 6545-6552; Fulop, F.; Pihlaja, K.; Mattinen, J.; Bernath, G. *J. Org. Chem.* **1987**, 52, 3821-3825.
7. Seebach, D.; Aebi, J. D. *Tetrahedron Lett.* **1984**, 25, 2545-2548.
8. Jeong, Y.-C.; Anwar, M.; Nguyen, T. M.; Tan, B. S. W.; Chai, C. L. L.; Moloney, M. G. *Org. Biomol. Chem.* **2011**, 9, 6663-6669.
9. Fulop, F.; Pihlaja, K.; Neuvonen, K.; Bernath, G.; Argay, G.; Kalman, A. *J. Org. Chem.* **1993**, 58, 1967-1969.

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11. Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2708-2748.

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13. Corey, E. J.; Reichard, G. A. *J. Am. Chem. Soc.* **1992**, 114, 10677-10678.

14. Jeong, Y.-C.; Moloney, M. G. *Synlett*. **2009**, 2487-2491

15. Dyer, J.; Keeling, S.; King, A.; Moloney, M. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2793-2804; Bailey, J. H.; Cherry, D. T.; Crapnell, K. M.; Moloney, M. G.; Shim, S. B.; Bamford, M.; Lamont, R. B. *Tetrahedron* **1997**, 53, 11731-11744.

16. Li, W.-R.; Lin, S. T.; Hsu, N.-M.; Chern, M.-S. *J. Org. Chem.* **2002**, 67, 4702-4706.

17. Jones, K.; Keenan, M.; Hibbert, F. A. *Synlett* **1996**, 509-510.

18. Palatinus, L.; Chapuis, G. *J. Appl. Cryst.* **2007**, 40, 786-790.

19. Parois, P.; Cooper, R. I.; Thompson, A. L. *Chem. Cent. J.* **2015**, 9, 1-14; Cooper, R. I.; Thompson, A. L.; Watkin, D. J. *J. Appl. Cryst.* **2010**, 43, 1100-1107.