Enantiomerically Pure 3–Substituted 2–Phenylprolines by Caesium Fluoride / Tetramethoxysilane Mediated 1,4– Addition of 3(*S*)–5(*R*)–Diphenylmorpholin–2–one to Acrylates

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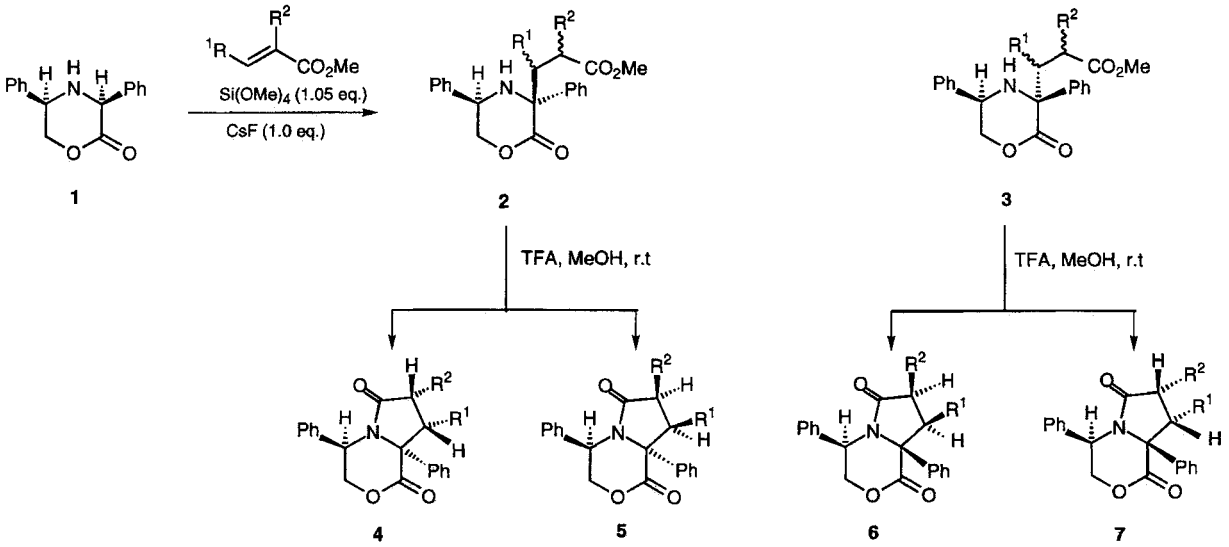
Development of methodology for the asymmetric synthesis of non–proteinogenic amino acids has become a priority.[1] The driving force behind much of this work is the desire to construct amino acid analogues capable of acting as conformational constraints in order to probe the relationship between peptide tertiary conformation and bioactivity.[2] Proline analogues have been found to exert particular conformational constraints in peptides, due to introduction of a high barrier to conformer interconversion[3] and, in addition, find use as components of angiotensin–converting–enzyme inhibitors.[4] Despite the interest focused on the synthesis of α–substituted amino acids,[5] syntheses of α–substituted prolines are relatively scarce; notable routes including Seebach's self reproduction of chirality approach,[6] and diastereoselective alkylations of a chiral Schiff base,[7] or *cis*–(5–phenylthio)proline.[8] A recent report in which α–phenylproline[9] was used as a precursor for the synthesis of a selective NK1 receptor antagonist for substance P[10] highlighted the need to address the particular paucity of methods for obtaining enantiomerically pure α–phenylprolines.

α–Phenylproline derivatives have been prepared by cycloaddition of azomethine ylids generated from Schiff's bases to achiral[11] or chiral[12] dipolarophiles. We have shown that (3*S*,5*R*)–3,5–diphenylmorpholin–2–one **1** can be used to access α–phenylproline derivatives using our azomethine ylid chiral relay strategy,[13] and became interested in **1** as a means of providing more general access to such structures. To this end, we decided to investigate combination of **1** with the caesium fluoride / tetraalkoxysilane system, reported by Corriu to promote 1,4–additions of ketones to Michael acceptors under very mild conditions (neat, room temperature),[14] although we were aware of later work which had demonstrated that this reagent system also promoted *N*–conjugate addition of amides to Michael acceptors.[15] In the event, we found that simply mixing equimolar amounts of **1** with caesium fluoride, tetramethoxysilane and methyl acrylate and allowing the mixture to stand for 1h[16] resulted in smooth formation of an inseparable mixture of Michael adducts **2**, and **3** (R^1, R^2 = H)[17] in 1 : 1 ratio (**Scheme 1**) which were converted to the separable lactams **4a** and **6a** in 40% yield for each using methanolic trifluoroacetic acid (**Scheme 1**). Of greater interest was the observation that methyl *E*–butenoate gave only two of the four possible diastereoisomeric products in a diastereoisomeric ratio of 6 : 1 whose relative stereochemistries were shown by subsequent conversion to amides **4b** and **6b** (*vide infra*). Likewise, methyl cinnamate furnished, a major adduct, isolated in 58% yield, accompanied by lesser amounts of the other three possible diastereomers (*ca* 6% of each). NOE difference studies indicated the major isomer to be **4c** having the same relative stereochemistry as that formed from methyl *E*–butenoate corresponding approximately to facial selectivity.[17] A similar, although reduced, facial selectivity was observed with methyl methacrylate



1 2 3 4 5 6 7

	R^1	R^2	Isolated yield over two steps(%)			
a	H	H	41		41	
b	Me	H	66	–	12	–
c	Ph	H	58	7	6	6
d	H	Me	30	30	10	10

Scheme 1

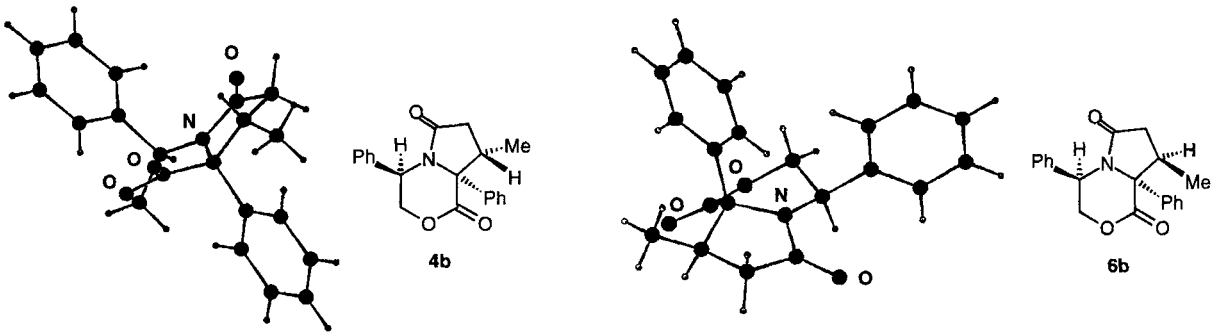


Figure 1

although no diastereoselectivity was observed at C–2 of the side chain, as evidenced by two pairs of lactams being isolated in a 3 : 1 ratio **4d** + **5d** : **6d** + **7d**.

Although it was possible to separate some of the mixtures of adducts, it was generally found experimentally simpler to isolate pure material after cyclisation to the corresponding bicyclic lactams. X–ray crystallographic analysis confirmed the structures of the lactams **4b** and **6b** (**Figure 1**).[18]

The mildness of the conditions, lack of *N*–protection and high conversions, coupled with the moderate but useful facial selectivity and diastereoselectivity in the case of *E*–3–substituted acrylates mean that this approach provides an alternative to the usual enolate–based alkylation of morpholinone systems.[19]

The facial selection causing inversion at C–3 is in keeping with previously observed diastereocontrol in alkylations of such systems.[19] A tentative explanation for the C–3/C–1 diastereocontrol observed can be put forward based upon X–ray spectroscopic analysis[18] which clearly indicates that **1** exists as a *quasi*–chair unlike related *N*–substituted systems[19b] (**Figure 2**).

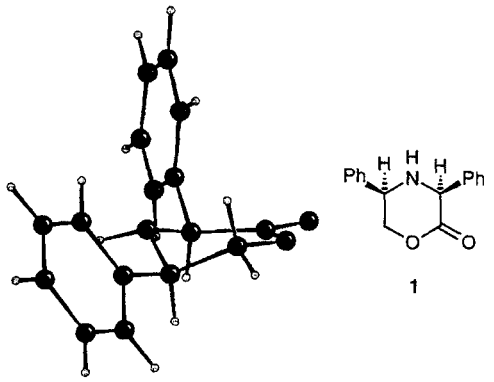
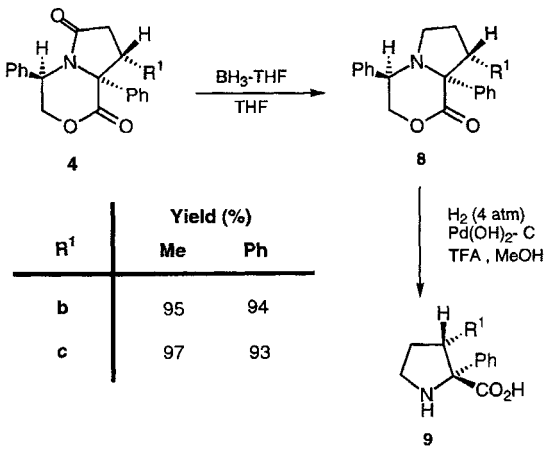


Figure 2

Applying Corriu's mechanistic rationale to the silyl ketene acetal derivative of **1** as a flattened chair and placing the 3–*E*–substituent of the Michael acceptor in the sterically least demanding environment leads to the observed major diastereomer (**Figure 3**).

In the cases where a major adduct was obtained (**4b**, **4c**) the lactam ring was chemoselectively reduced to furnish the corresponding pyrrolidines **8** in near quantitative yield using BH_3:THF and the morpholinone template was subsequently degraded using standard hydrogenolysis conditions[13] to furnish the *syn*–disubstituted 2–phenylproline derivatives **9** in excellent. It is noteworthy that hydrogenolytic cleavage of the benzylic α–amino acid was not observed, in keeping with our previous observations.[13]



R¹	Yield (%) Me	Ph
b	95	94
c	97	93

Scheme 2

In conclusion, we have demonstrated a mild means of alkylating 3,5–diphenylmorpholinone **1** and have demonstrated that the corresponding Michael adducts may be converted to enantiomerically pure α–phenylproline derivatives.

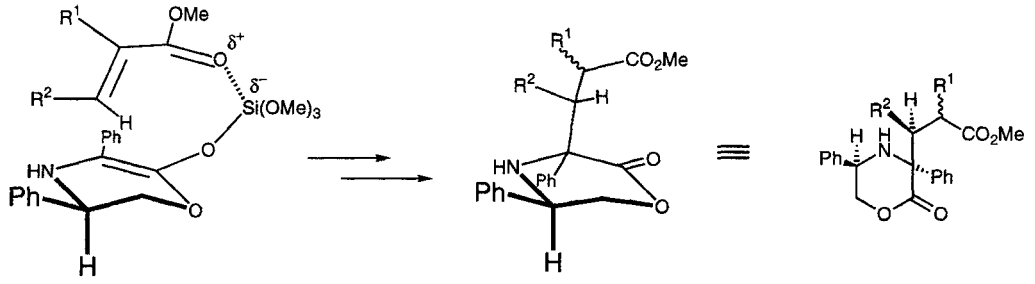


Figure 3

Acknowledgements

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References

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16. **General procedure for alkylation.**
The Michael acceptor (1.1 mmol) was added dropwise, to a suspension of morpholinone **1** (253 mg, 1 mmol), CsF (152 mg, 1 mmol), and $Si(OMe)_4$ (150 μL, 1 mmol), at room temperature under an argon atmosphere. After stirring for 1 hour, the reaction mixture was directly subjected to flash column chromatography on silica gel (eluent: ethyl acetate / petroleum ether = 2:8 by volume) to afford the corresponding mixture of diastereoisomers as a colourless oil.
General procedure for formation of lactams.
The mixture of diastereoisomers (1 mmol) and trifluoroacetic acid (2 mL) in methanol (70 mL) was refluxed with stirring under nitrogen for 72 hours. The reaction mixture was allowed to cool and the trifluoroacetic acid was neutralised with $NaHCO_3$. The mixture was filtered and the solvent removed *in vacuo*, then purified by silica gel (gradient elution petroleum ether / ethyl acetate = 8:2 to 6:4) to furnish the cyclised material.
General procedure for reduction of lactams.
To a solution of starting material (**7**) (321 mg, 1 mmol) in THF (15 mL) under a nitrogen atmosphere, was added a solution of 1.0 M diborane in THF (3mL) dropwise over 10 minutes. The temperature was maintained at approximately 0 °C during the addition and the solution was then refluxed for 90 minutes. The flask was allowed to cool to room temperature. 1N HCl (4mL) was added and the solvent removed *in vacuo*. Subsequently a solution of 1 M NaOH was added until the mixture reached pH 12. The mixture was extracted with ether (3 x 20 mL), the combined extracts dried over MgSO4, and the solvent removed *in vacuo*. The crude residue was purified by chromatography on silica (eluent petroleum ether / ethyl acetate = 1 / 9) to afford the pure reduced material.
General procedure for hydrogenolytic-degradation of the morpholinone template.
The starting material (0.33 mmol) was dissolved in MeOH (40 mL). Palladium hydroxide on carbon (50 mg) and TFA (60μL) were added and the mixture was stirred under a hydrogen atmosphere (4 atm) at room temperature overnight. The catalyst was removed by filtration through Celite and the solvent removed *in vacuo* to afford the product.
17. **Illustrative spectroscopic data:**
4a: yield 41%. mp: 268-269 °C. $[\alpha]_D^{23}$ +27.0 (c = 1, $CHCl_3$). IR (Film): 2948, 1746, 1704, 1209, 698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.44 (m, 3H), 2.98 (m, 1H), 4.17.(d, *J* = 11.7 Hz, 1H), 4.38 (dd, *J* = 3.6 Hz, 11.7 Hz, 1H), 5.17 (d, *J* = 3.6 Hz, 1H), 7.07-7.59 (m, 10H, Ar). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.62 (CH_2), 34.47 (CH_2), 53.54 (CH), 68.40 (C), 70.16 (CH_2), 124.38-137.59 (10 Carbons, Ar), 170.59 (C), 173.98 (C). $^m/_z$ (CI, NH_3) 308 (100%, MH^+). Anal. Calc. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56, found C, 74.49; H, 5.56; N, 4.68.
6a: yield 41%. mp 177-178 °C; $[\alpha]_D^{23}$ -0.7 (c = 0.8, $CHCl_3$); IR (Film): 2953, 1757, 1723, 1205, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.50 (dd, *J* = 3.1 Hz, 16.7 Hz, 1H), 2.87 (dd, *J* = 8.3 Hz, 16.7 Hz, 1H), 3.39 (dd, *J* = 3.1 Hz, 8.3 Hz, 1H), 3.77 (s, 3H), 4.20 (t, *J* = 12.0 Hz, 1H) 4.43 (dd, *J* = 5.2 Hz, 12.0 Hz, 1H), 5.18 (dd, *J* = 5.2 Hz, 12.0 Hz, 1H), 7.33-7.57 (m, 10H, Ar); $^m/_z$ (CI, NH_3) 366 (100%, MH^+); Anal. Calc. for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83, found C, 68.75; H, 4.99; N, 3.67.
4b: yield 66%, mp 162-163 °C. $[\alpha]_D^{23}$ -2.2 (c = 1, $CHCl_3$); IR (Film): 3012, 2971, 1761, 1707, 1371, 1211, 759, 703 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.7 Hz, 3H), 2.17 (dd, *J* = 6.8 Hz, 11.1 Hz, 1H), 2.52 (dd, *J* = 8.1 Hz, 17.0 Hz, 1H), 3.26 (m, 1H), 4.07.(d, *J* = 12.0 Hz, 1H), 4.23 (dd, J = 3.5 Hz, 12.0 Hz, 1H), 5.05 (d, *J* = 3.5 Hz, 1H), 7.17-7.48 (m, 10H); $^m/_z$ (CI, NH_3) 322 (100%, MH^+); Anal. Calc. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36, found C, 74.46; H, 5.85; N, 4.35.
4c: yield 58%. mp: 218-219 °C; $[\alpha]_D^{23}$ -110.1 (c = 1, $CHCl_3$); IR (KBr): 3035, 2918, 1762, 1703, 1376, 1222, 731, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.74 (dd, *J* = 9.0 Hz, 17.5 Hz, 1H), 2.88 (dd, *J* = 12.3 Hz, 17.5 Hz, 1H), 4.12 (d, *J* = 11.9 Hz, 1H), 4.30 (dd, *J* = 3.6 Hz, 11.9 Hz, 1H), 4.54 (dd, *J* =9.0 Hz, 12.3 Hz, 1H), 5.17 (d, *J* = 3.6 Hz, 1H), 6.41 (m, 1H), 6.94-7.52 (m, 14H); NOE data: **H5** → C5–phenyl *ortho*–H (14%), C3–phenyl *ortho*–H (3.5%); **H1'** → C1'–phenyl *ortho*–H (14%), H2'β (8%); **H2'**β→ C1'–phenyl *ortho*–H (21%); $^m/_z$ (CI, NH3) 384 (100%, MH^+); Anal. Calc. for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.65, found C, 78.03; H, 5.43; N, 3.70.

4d: yield 30%. mp 98-99 °C; $[\alpha]_D^{23}$ -26.5 (c = 1, $CHCl_3$); IR (KBr): 2968, 1761, 1701, 1369, 1201, 741, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.20 (d, *J* = 6.2 Hz, 3H), 2.63 (m, 3H), 4.16.(d, *J* = 11.7 Hz, 1H), 4.40 (dd, *J* = 3.6 Hz, 11.7 Hz, 1H), 5.18 (d, *J* = 3.6 Hz, 1H), 7.14-7.48 (m, 10H); NOE data: **H2'** → C5–phenyl *ortho*–H (3%), H1'β (8.5%) Me (9%); **Me** → H2' (16.5%) H1'α (7%) C3–phenyl *ortho*–H (7.5%); **H1'β** → H1'α (29%) H2' (10.5%) C5–phenyl *ortho*–H (4%); *m/z* (CI, NH_3) 322 (100%, MH^+).

5d: yield 30%. mp 191-192 °C; $[\alpha]_D^{23}$ -8.8 (c = 1, $CHCl_3$); IR (KBr): 2982, 1749, 1703, 1379, 1212, 737, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.7 Hz, 3H), 2.15 (dd, *J* = 2.2 Hz, 13.7 Hz, 1H), 2.65 (m, 1H), 3.36 (dd, *J* = 10.6 Hz, 13.7 Hz, 1H), 4.15.(d, *J* = 12.0 Hz, 1H), 4.42 (dd, *J* = 4.1 Hz, 12.0 Hz, 1H), 5.15 (d, *J* = 4.1 Hz, 1H), 7.18-7.48 (m, 10H); *m/z* (CI, NH_3) 322 (100%, MH^+); Anal. Calc. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36, found C, 74.44; H, 6.26; N, 4.45.

8b: yield 95%. mp: 104-105 °C; $[\alpha]_D^{23}$ -4.2 (c = 1.0, $CHCl_3$); IR (KBr): 2963, 1740, 1178, 704 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.8 Hz, 3H), 1.65 (m, 2H), 1.97 (m, 2H), 2.89 (m, 1H), 3.02 (m, 2H), 4.29 (d, *J* = 4.1 Hz, 2H), 4.46 (t, *J* = 4.1 Hz, 1H), 7.24-7.52 (m, 10H); *m/z* (CI, NH_3) 308 (100%, MH^+); Anal. Calc. for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56, found C, 78.03; H, 6.96; N, 4.56.

8c: yield 94%. mp: 103-104 °C; $[\alpha]_D^{23}$ -91.0 (c = 1, $CHCl_3$); IR (Film): 3032, 2844, 1746, 1164, 1079, 734, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.26 (m, 2H), 3.22 (m, 2H) 4.15 (dd, *J* = 7.1 Hz, 11.2 Hz, 1H), 4.39 (d, *J* = 4.2 Hz, 2H), 4.61 (t, *J* = 4.2 Hz, 1H), 6.95-7.50 (m, 15H); *m/z* (CI,NH_3) 370 (100%, MH^+); Anal. Calc. for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.28; N, 3.79, found C, 80.99; H, 6.59; N, 3.88.

9b: yield 97%. mp: 209-210 °C; $[\alpha]_D^{23}$ -14.7 (c = 0.65, MeOH); IR (KBr): 3500-2300, 3436, 3059, 2980, 1634, 1355, 700 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ = 0.92 (d, J = 6.8 Hz, 3H), 1.96 (m, 1H), 2.23 (m, 2H), 3.40 (m, 1H), 3.59 (m, 2H), 7.32-7.46 (m, 5H); *m/z* (Electrospray) 206 (100%, MH^+); HRMS for $C_{12}H_{16}NO_2$ requires 206.1181, found: 206.1184

9c: yield 93%. mp: 173-174 °C; $[\alpha]_D^{23}$ -36.4 (c = 0.5, MeOH); IR (KBr): 3440-2300, 3422, 3030, 1641, 1343, 703 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ = 2.25 (m, 1H), 2.57 (m, 1H), 3.65 (m, 1H), 3.73 (m, 1H), 4.54 (m, 1H), 6.87-7.48 (m, 10H); *m/z* (Electrospray) 268 (100%, MH^+); HRMS for $C_{17}H_{18}NO_2$ requires 268.1338, found: 268.1338

18. Crystal data: **4b**: $C_{20}H_{19}NO_3$ M = 321.4, monoclinic, *P*21c *a* = 9.677, *b* = 10.204, *c* = 17.490 Å, *V* = 1694.5 $Å^3$, *Z* = 4. 3284 Independent reflections were collected and 2101 reflections with $I > 3\sigma(I)$ were used in the analysis. Final *R* = 3.92, final Hamiltonian weighted *R* = 5.46.
Crystal data for **6b**: $C_{20}H_{19}NO_3$ M = 321.4, monoclinic, *P*21c *a* = 8.223, *b* = 14.143, *c* = 14.447 Å, *V* = 1678.3 $Å^3$, *Z* = 4. 3281 Independent reflections were collected and 2327 reflections with $I > 3\sigma(I)$ were used in the analysis. Final *R* = 3.66, final Hamiltonian weighted *R* = 5.03.
Crystal data for **1**: $C_{16}H_{15}NO_2$ M = 253.3, triclinic, *P*1 *a* = 6.131, *b* = 9.825, *c* = 11.567 Å, *V* = 663.2 $Å^3$, *Z* = 2. 2592 Independent reflections were collected and 2353 reflections with $I > 3\sigma(I)$ were used in the analysis. Final *R* = 5.63, final Hamiltonian weighted *R* = 7.04. Data for crystallographic analyses were measured ($2\theta_{max}$ = 144°) on an Enraf–Nonius CAD–4 diffractometer using Cu–K_a radiation ω–2θ scans. The structures were solved by direct methods and refined by least squares using the CRYSTAL package. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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