Stereospecific Synthesis of Exo-Trisubstituted Olefins. The Highly Efficient Synthesis of Carbacyclins

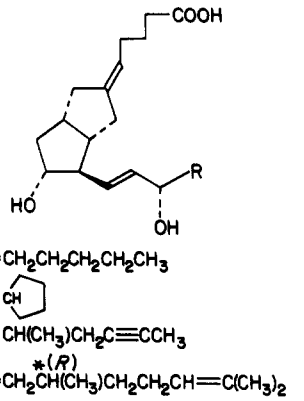
Summary: The simple synthesis of carbacyclin and analogues is described in which the stereospecific 1,4-hydrogenation of a 1,3-diene to an internal monoene plays a key role.

Sir: One of the biggest synthetic problems awaiting solution in the PG field is how to achieve the stereospecific synthesis of carbacyclin (**1**). Some carbacyclin analogues (**2**–**4**),[1] modified in the lower side chain, are intravenous and orally active PGI_2 derivatives which may be of therapeutic value for occlusive peripheral vascular diseases, etc.[2] Although more than ten groups have succeeded in the synthesis of these important compounds, none of the syntheses has involved the stereospecific formation of the 5-*E*-trisubstituted olefin (PG numbering).[3] Accordingly, extremely troublesome separation of the stereoisomers (5-*E* and 5-*Z*) is unavoidable in all the syntheses known, making the industrial-scale preparation of carbacyclins fairly difficult. In this communication we report a solution to this serious synthetic problem, which allows the simple preparation of carbacyclins (Scheme I).

Retrosynthetic analysis of carbacyclins suggested to us that the conjugated diene (**6** or **8**) would be stereospecifically converted to the exo-trisubstituted olefin (**7** or **9**), the key intermediate for carbacyclins, by the 1,4-hydrogenation. Stereospecific hydrogenation of 1,3-dienes to internal monoenes by $ArM(CO)_3$ compounds as catalysts has been extensively studied over the past ten years.[4] However, few applications to the syntheses of rather complex molecules have been reported.[5]

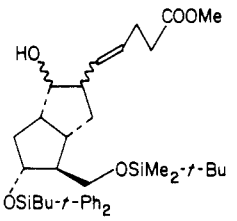
In the first place, the 1,4-hydrogenation of the conjugated diene **6** with the *E*-disubstituted olefin, the more promising intermediate on the basis of the mechanistic grounds of the hydrogenation,[6] was undertaken (Scheme II). Toward this end, 1,3-diene **6**, $[\alpha]^{20}_D$ −46° (*c* 1.96, MeOH), was stereospecifically synthesized from the well-known Corey lactone in ca. 27% overall yield. Namely, the homoallylic alcohol **5** obtainable from the Corey lactone by using the intramolecular thermal ene reaction as a key step[7] was converted to **6** in one pot (i, methanesulfonyl chloride–triethylamine in toluene; ii, DBU). The NMR spectrum of **6** in $CDCl_3$ solvent showed one proton doublet (H_a, δ 6.25, J = 16.5 Hz), indicating the stereochemical homogeneity of **6** (4-*E*). Stereospecific hydrogenation of **6** was investigated under the various reaction conditions. Among the conditions examined, hydrogenation of **6** in acetonitrile (70 atm of H_2 pressure, 130 °C, 12 h) using (methyl benzoate)$Cr(CO)_3$ as a catalyst (0.2 molar equiv to the substrate) afforded the desired product **7** stereospecifically, $[\alpha]^{20}_D$ −17° (*c* 1.32, $CHCl_3$), though in modest yield (84% based on the recovery of **6**, 21%). A much better result was obtained by the use of acetone as a solvent in place of acetonitrile. Treatment of **6** with a catalytic amount of (methyl benzoate)$Cr(CO)_3$

Scheme I



1, R = $CH_2CH_2CH_2CH_2CH_3$
2, R =
3, R = $CH(CH_3)CH_2C{\equiv}CCH_3$
4, R = $CH_2\overset{*(R)}{C}H(CH_3)CH_2CH_2CH{=}C(CH_3)_2$

Scheme II



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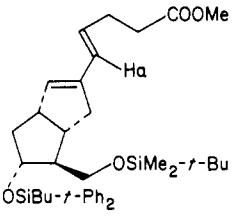

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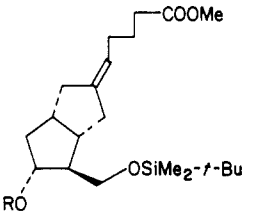
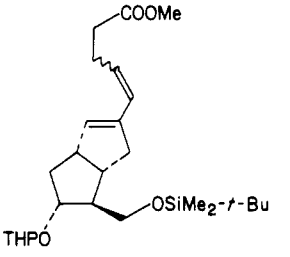


7, R = Si-t-BuPh$_2$
9, R = THP



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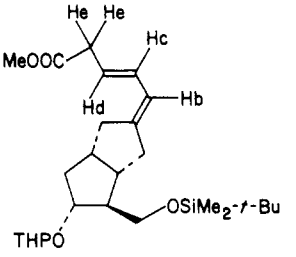

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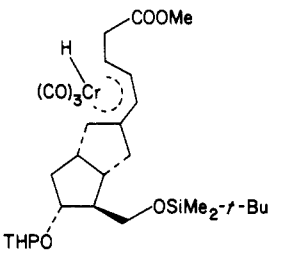

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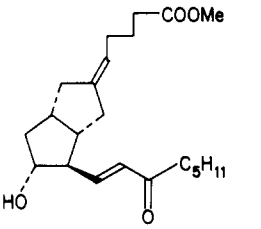

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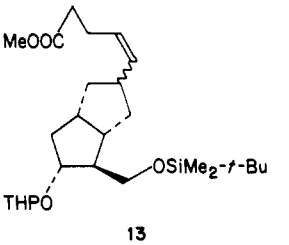

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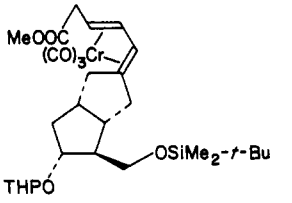

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(1) Carbacyclin analogues are called carbacyclins in this paper.
(2) For example: Kawasaki, A. "Abstracts of Papers", Fifth International PG Conference, Florence, 1982, p 313.
(3) Bartman, W.; Beck, G. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 751.
(4) Farona, M. F. "Organometallic Reactions and Syntheses"; Plenum Press: New York and London, 1977, Vol. 6, pp 223–288.
(5) To the best of our knowledge, one application to the synthesis of rather complex molecules is known, see: Rosenmund, P.; Casutt, M. *Tetrahedron Lett.* **1983**, *24*, 1771.
(6) The most favorable stereochemistry for reduction of conjugated dienes is *E,E*, then, *Z,E*, with the least favorable being *Z,Z*. In the case of conjugated dienes (*Z,E* and *Z,Z*), the isomerization generally takes place through a 1,5-hydrogen shift to afford isomeric monoenes. See ref 4.
(7) Ogawa, Y.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 1067.

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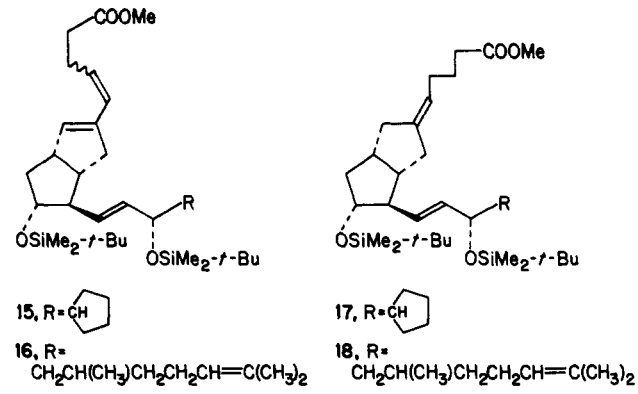
(0.2 molar equiv) in acetone under 70 atm of H_2 pressure (120 °C, 15 h) provided **7** in nearly quantitative yield. The stereochemistry of **7** was determined by comparison with authentic materials[8] on the basis of the GLC analysis, indicating the absence of the 5-*Z* stereoisomer. Thus the stereospecific formation of the 5-*E*-trisubstituted olefin in carbacyclins has been realized for the first time.[9]

Next we turned our attention to the 1,4-hydrogenation of the *Z*-rich 1,3-diene **8** (*E*:*Z* = 1:2.2), since **8** was much more efficiently obtainable from the Corey lactone in 55% overall yield.[10] As was expected, hydrogenation of **8** in acetonitrile (70 atm of H_2 pressure, 130 °C, 12 h) using (methyl benzoate)$Cr(CO)_3$ as a catalyst (0.2 molar equiv) gave two products. One was the desired 1,4-reduction product **9**[11] (28%), and the other was the exo-conjugated diene **10** (27%), probably formed through a 1,5-hydrogen shift. In addition the starting diene containing only the 4-*Z* stereoisomer was recovered (37%). This result strongly implied the fact that while one part of the conjugated diene **8** (4-*Z*) afforded the undesired product **10**[12] probably via the intermediate **11**, the 4-*E* isomer was exclusively hydrogenated to give the desired product **9**. This difficulty in the hydrogenation has been fully overcome by using two other reaction conditions. Firstly, hydrogenation of **8** in acetone (70 atm of H_2 pressure, 120 °C, 15 h) using (methyl benzoate)$Cr(CO)_3$ as a catalyst (0.2 molar equiv) provided the desired product **9**[13] in 95% yield without formation of the exo-conjugated diene **10**. Secondly, even in the case of acetonitrile solvent, simple increase in H_2 pressure to 130 atm afforded only the desired product **9** in 83% yield. Thus, the stereospecific synthesis of the key intermediate **9** for carbacyclins has been accomplished in 50–55% overall yield from the Corey lactone, offering the most efficient synthetic route to carbacyclins.[14] The key intermediate **9** was transformed to the hydroxy enone **12**, $[\alpha]^{20}_D$ +53° (*c* 0.77, MeOH), in four steps (79% overall yield). Also at this stage the absence of the 5-*Z* stereoisomer was confirmed.[8]

It is quite interesting to clarify why the exo-conjugated diene **10** or its 1,4-reduction product **13** was not formed from **8** under the reaction conditions just mentioned above. We assumed the following mechanism. Under all the hydrogenation conditions used, the diene **8** (4-*Z*) and the exo-conjugated diene **10** might be in a state of equilibrium through the intermediate **11**.[15] However, owing to the extremely facile hydrogen abstraction from the coordinated diene **14**, the 1,4-hydrogenation of **10** to **13** might be thoroughly prevented. Thus, the 5-*E*-trisubstituted olefin **9** might be exclusively formed under the well-suited hydrogenation conditions. This assumption was strongly supported by the experimental fact that hydrogenation of the exo-conjugated diene **10** in acetone using (methyl benzoate)$Cr(CO)_3$ as a catalyst (0.2 molar equiv) (70 atm of H_2 pressure, 120 °C, 16 h) gave the 5-*E*-trisubstituted olefin **9** as the sole product in 94% yield.

Scheme III



Even in the case of the conjugated dienes (**15** and **16**) having the ω-chain, stereospecific 1,4-hydrogenation proceeded quite smoothly (Scheme III). Namely, the diene **15** (*E*:*Z* = 1:2.2) prepared from **8** in six steps (ca. 44% overall yield[16]) underwent hydrogenation in acetone [0.2 molar equiv of (methyl benzoate)$Cr(CO)_3$, 70 atm of H_2 pressure, 120 °C, 15 h], giving the desired product **17** stereospecifically in quantitative yield. The hydrogenated product **17** was then converted to OP-41483 (**2**),[2] one of the therapeutically useful carbacyclins, in two steps (84% yield). Likewise, the diene **16** (*E*:*Z* = 1:2.2) obtainable from **8** in six steps (ca. 34% overall yield[17]) was also converted to **18**, the precursor of CS-570,[2] stereospecifically in quantitative yield.[18]

At the conclusion of this communication we mention that the synthesis presented in this paper offers the most efficient synthetic route to carbacyclins, which will make the industrial-scale preparation of these therapeutically useful compounds much simpler.

(8) Authentic materials (5-*E* and 5-*Z*) were prepared according to the method reported by M. Hayashi et al., see: Konishi, Y.; Kawamura, M.; Iguchi, Y.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, *37*, 4391.

(9) The key intermediate **7** was converted to OP-41483 **2** (40% overall yield) and its stereoisomer at C-15 (15%) in six steps.

(10) Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1984**, 579.

(11) Stereochemistry of **9** was determined by comparison with authentic materials on the basis of the GLC analysis. See ref 8.

(12) Stereochemistry of **10** was determined by the following facts. The NMR spectrum of **10** in $CDCl_3$ solvent showed one proton d × d (H_c, δ 6.25, *J* = 15.5, 11 Hz), one proton d (H_b, δ 5.96, *J* = 11 Hz), one proton d × t (H_d, δ 5.64, *J* = 15.5, 7 Hz), and two protons d (H_a, δ 3.13, *J* = 7 Hz), strongly indicating the presence of the *E*-disubstituted olefin. Furthermore, **10** was converted to **9** through the intermediate **8** (4-*Z*) in quantitative yield by the 1,4-hydrogenation reaction. Thus, stereochemistry of the trisubstituted double bond in **10** was determined to be *E*.

(13) Hydrogenation of **8** in acetone (70 atm of H_2 pressure, 120 °C, 15 h) using (toluene)$Cr(CO)_3$ as a catalyst (0.2 molar equiv) also afforded **9** stereospecifically in 81% yield.

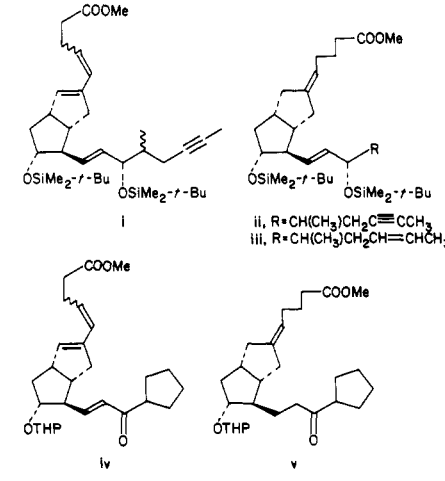
(14) The intermediate **9** can be easily converted to carbacyclins 1–4. See ref 3.

(15) The exo-conjugated diene **10** was formed (28%) just by heating **8** in the presence of a catalytic amount of (methyl benzoate)$Cr(CO)_3$ (0.2 molar equiv) (acetone, argon atmosphere, 130 °C, 25 h). Likewise, the conjugated diene **8** (4-*Z*) was formed from **10** under the same conditions mentioned above (38%).

(16) In addition to **15**, the 15β-isomer was obtained (21%). The yield is not optimized.

(17) The 15β-isomer was also obtained (27%). The yield is not optimized.

(18) Partial reduction of triple bonds is an important pathway of the present 1,4-hydrogenation reaction. Namely, from the diene **i**, both of the desired product **ii** (35%) and the undesired product **iii** (51%) were obtained. Furthermore, in the case of the enone **iv**, the saturated ketone **v** was formed exclusively (100%).



Supplementary Material Available: Full NMR data for compounds 5–10 and 15–18 (1 page). Ordering information is given on any current masthead page.

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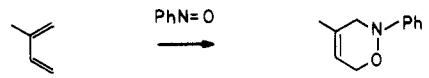
Received June 18, 1984

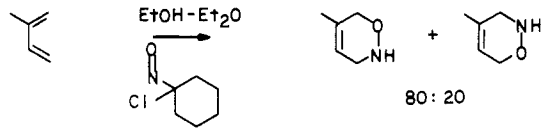
Regioselectivity in the Intermolecular Diels–Alder Reaction of Acyl Nitroso Compounds (*C*-Nitrosocarbonyl Compounds) and Nitrosoformates (*O*-Nitrosocarbonyl Compounds)

Summary: A study of the regioselectivity of the intermolecular Diels–Alder reaction of (nitrosocarbonyl)benzene and methyl nitrosoformate with representative electron-rich and electron-deficient 2-substituted-1,3-cyclohexadienes is described.

Sir: The orientation of the intermolecular Diels–Alder addition of aryl nitroso compounds with dienes has been investigated in detail and a rationalization of the observed regioselectivity has been presented on the basis of consideration of the relative stabilization of the two possible dipolar transition states.[2,3] The predicted and observed product in the cycloaddition of nitrosobenzene with isoprene is shown in eq 1. By contrast, a study of re-

(1) 

gioselectivity of the addition of nitrosobenzene with β-myrcene, a 2-alkyl-substituted-1,3-butadiene, revealed a marked dependence on reaction temperature and solvent.[4] Similarily, the observed, though not predicted, product of the addition of α-chloronitrosocyclohexane with isoprene, eq 2, possesses the reversed orientation of addition.[5] In

(2) 

the absence of a better rationalization this reversal in regioselectivity has been attributed to steric factors despite the fact that such effects must be relatively removed from the reaction centers.

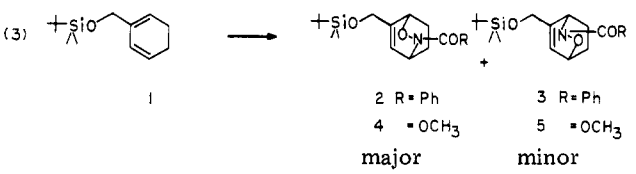
Herein, we detail a study of the orientation of the intermolecular[2,6] Diels–Alder reaction of acyl nitroso compounds, (nitrosocarbonyl)benzene and methyl nitrosoformate, with weakly electron-rich and electron-deficient 2-substituted-1,3-cyclohexadienes.[2,6] The observed results, detailed in eq 3 and 4 and Table I, are consistent with the prediction that nitrosocarbonyl compounds behave as well-defined electron-deficient 2π components in a normal ($HOMO_{diene}$ controlled)[7] Diels–Alder reaction with electron-rich 2-substituted dienes *and* additionally illustrate that they may serve as useful 2π components in regioselective Diels–Alder reactions with electron-deficient 2-substituted-1,3-cyclohexadienes. The latter results are consistent with either a normal ($HOMO_{diene}$ controlled) or inverse electron demand ($LUMO_{diene}$ controlled)[7] Diels–Alder reaction.

Table I. Diels–Alder Reaction of Nitrosocarbonyl Compounds with 2-Substituted 1,3-Cyclohexadienes

substrate	conditions[a]	product(s)	% yield[b]
1	A, CH_2Cl_2, 25 °C, 1 h	2/3	45/16
	0 °C, 1 h		31/24
	A, DMF, 25 °C, 3 h		23/5
	0 °C, 3 h		30/13
	B, CH_2Cl_2, 40 °C, 5 h		11/4
	B, C_6H_6, 60 °C, 5 h		43/12
1	C, CH_2Cl_2, 25 °C, 1 h	4/5	72 (50/16)[c]
6	A, CH_2Cl_2, 25 °C, 1 h	7/8	47/16
	A, DMF, 25 °C, 3 h		47/16
6	C, DMF, 25 °C, 3 h	9/10	30/11

[a] A: Benzoyl hydroxamic acid[12a] (2.2 equiv) was added dropwise to a solution of diene and $(n\text{-Bu})_4NIO_4$[12b] (2.31 equiv). B: A solution of diene and the (nitrosocarbonyl)benzene–9,10-dimethylanthracene adduct[3,6] (1.1 equiv) was warmed at the described temperature. C: Methyl *N*-hydroxycarbamate[12c] (2.2 equiv) was added dropwise to a solution of the diene and $(n\text{-Bu})_4NIO_4$[12b] (2.31 equiv). [b] All products exhibited the expected ^1H NMR, IR, and MS characteristics consistent with the assigned structure and gave satisfactory C, H, N analysis or HRMS information. All yields (ratios) are based on purified, separated material isolated by chromatography (SiO_2). [c] The inseparable, purified adducts 4/5 (72% combined yield) were deprotected; 1.2 equiv of $(n\text{-Bu})_4NF$, THF, 25 °C, 30 min; and the isomeric alcohols were separated (50% and 16% yield, respectively) and fully characterized.

Thermal cycloaddition of (nitrosocarbonyl)benzene and methyl nitrosoformate with the weakly electron-rich 2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-cyclohexadiene (1) afforded predominately the para[8] adducts 2 and 4. The

(3) 

structure of 2, the major regioisomer of the addition of (nitrosocarbonyl)benzene with 2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-1,3-cyclohexadiene (1), was confirmed by X-ray analysis.[9] The identification of 4, the major

(1) (a) Searle Scholar recipient, 1981–85. National Institutes of Health research career development award recipient, 1983–1988 (CA 00898). (b) Undergraduate research participant.

(2) For reviews including Diels–Alder reactions of electrophilic *C*-nitroso compounds, see: Kirby, G. W. *Chem. Soc. Rev.* **1977**, *6*, 1. Weinreb, S. M.; Staib, R. R. *Tetrahedron* **1982**, *38*, 3087.

(3) (a) Kresze, G.; Firl, J. *Fort. Chem. Forsch.* **1969**, *11*, 245. (b) Wichterle, D.; Kolinsky, M. *Chem. Listy* **1953**, *47*, 1787. Kresze, G.; Kosbahn, W. *Tetrahedron* **1971**, *27*, 1931. Kresze, G.; Saitner, H.; Kosbahn, W. *Ibid.* **1971**, *27*, 1941. Taylor, E. C.; McDaniel, K.; Skotnicki, J. S. *J. Org. Chem.* **1984**, *49*, 2500.

(4) Sasaki, T.; Eguchi, S.; Ishii, T.; Yamada, H. *J. Org. Chem.* **1970**, *35*, 4273. The addition of electron-withdrawing groups to the aryl nitroso compound accelerate the rate of cycloaddition and appear to reverse the observed regioselectivity, see: Givens, R. S.; Choo, D. J.; Merchant, Stitt, R. P.; Matuszewski, B. *Tetrahedron Lett.* **1982**, *23*, 1327 and ref 3a.

(5) Labaziewicz, H.; Riddell, F. G. *J. Chem. Soc., Perkin Trans 1* **1979**, 2926. Riddell, F. G. *Tetrahedron* **1975**, *31*, 523. Leonard, N. J.; Playtis, A. J.; Skoag, F.; Schmitz, R. Y. *J. Am. Chem. Soc.* **1971**, *93*, 3056. Leonard, N. J.; Playtis, A. J. *J. Chem. Soc., Chem. Commun.* **1972**, 133.

(6) For recent intramolecular acyl nitroso Diels–Alder reactions, see: Keck, G. E.; Nickell, D. G. *J. Am. Chem. Soc.* **1980**, *102*, 3632. Keck, G. E.; Fleming, S. A. *Tetrahedron Lett.* **1978**, 4763. Keck, G. E. *Tetrahedron Lett.* **1978**, 4767.

(7) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. Burnier, J. S.; Jorgensen, W. L. *J. Org. Chem.* **1983**, *48*, 3923.

(8) Alternatively, the major para adducts may be described as the "proximal" adducts and minor, meta adducts may be described as "distal" adducts. "Proximal" and "distal" refer to the relative orientation (distance) of the dienophile center of highest priority (nitroso oxygen) with the diene center of highest priority (substituted center of the cyclohexadiene). We thank a referee for suggesting this nomenclature.

(9) X-ray structure analysis was carried out on the free alcohol generated from 2 (1.2 equiv of $(n\text{-Bu})_4NF$, THF, 25 °C, 15 min, 74%) and was performed by Crystalytics Company, Lincoln, NE. Full details of the X-ray structure determination are provided in the supplementary material section.

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