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The unexpected formation of *trans-β-lactams* in the reaction of α-iminoesters (R-N=C(H)C(=O)OR') with diethylzinc. Crystal structure of *trans*-1-(N-t-butyl)-3-(N-t-butyl-N-ethylamino)-4-methoxycarbonylazetidin-2-one

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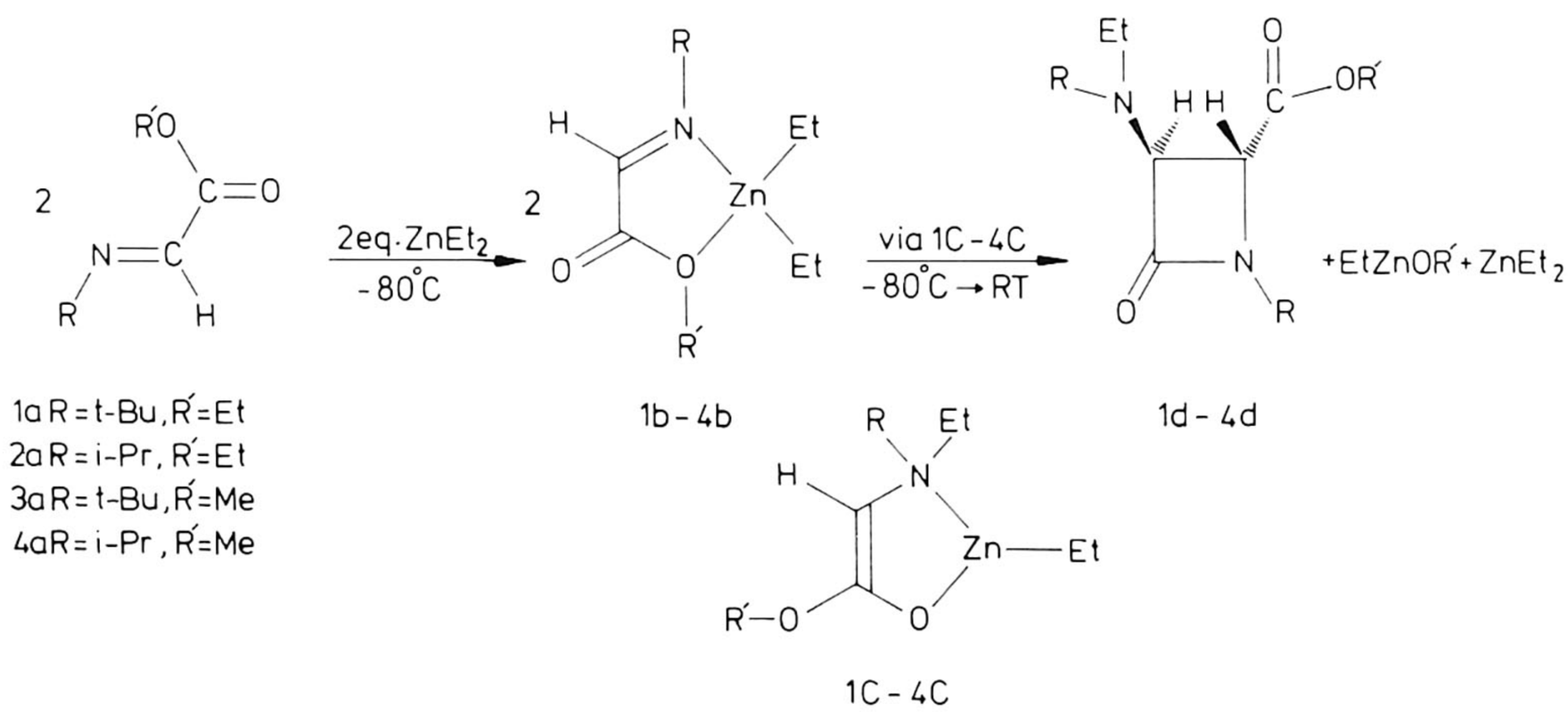
Abstract. Reaction of iminoesters, R-N=C(H)COOR', (R = t-Bu, i-Pr ; R' = Me, Et) with diethylzinc affords in a selective quantitative reaction *trans*-β-lactams. An X-ray crystal structure determination of the obtained *trans*-1-(N-t-butyl)-3-(N-t-butyl-N-ethylamino)-4-methoxy-carbonylazetidin-2-one has been carried out. The formation of the *trans*-β-lactams is believed to proceed via zinc enolates.

Recently, we developed a method for synthesizing 1,2-diamino-ethanes, 1-amino-2-imino-ethanes, α-hydroxy-imines and related organic compounds containing various substitution patterns which cannot be easily achieved *via* other routes. These compounds are formed upon hydrolysis of novel metal precursor complexes obtained from the reaction of substituted 1,4-dihetero-1,3-butadienes with dialkylzinc or trialkylaluminium compounds. These metal precursor complexes have, for example, been obtained from the reaction of R-N=C(R')C(R")=N-R with ZnR_2 [1,2,3] and with AlR_3 [3,4] or R-N=C(R')C(R")=O with ZnR_2 [5,6] and with AlR_3 [7,8]. Here we report the unexpected and selective synthesis of *trans*-β-lactams from the metal complexes formed between the α-iminoesters R-N=C(H)C(OR')=O (R = t-Bu, i-Pr; R' = Me, Et) and diethylzinc. The preparative route employed is outlined in Scheme 1.

Addition of diethylzinc (one equivalent) to a n-pentane solution of one of the α-iminoesters **1a-4a** at -80°C, resulted in the immediate precipitation of an orange-red solid. Most probably this precipitate is the σ-N,σ-O-complex of diethylzinc with the corresponding α-iminoester **1a-4a**.[9] However, when the temperature of the reaction suspensions was raised, the precipitated complex dissolved and finally yielded, at room temperature, a clear pale yellow solution. After hydrolysis and work-up, the isolated organic material was shown by ^{1}H-NMR spectroscopy[10,11] to be exclusively the *trans*-β-lactam **1d-4d**. Yields of **1d-4d** vary from 80 to 90% based on the α-iminoesters. Lactams **2d** and **4d** are oils at room temperature; **1d** and **3d** are colourless solids that were recrystallized from n-hexane to afford analytically pure samples.[12]

The β-lactams obtained are four-membered cyclic amides (the principal building blocks of naturally occurring and synthetic penicillins[19]) substituted with a dialkylamino group on C3 and an ester function on C4 in *trans*-positions. The amido nitrogen atom is substituted with a secondary or tertiary alkyl group. To prove unambiguously the *trans*-geometry of the formed



β-lactams, an X-ray crystal structure determination[14a] of **3d** was carried out. Final positional parameters are given in Table 1, bond distances and angles of the non-hydrogen atoms are given in Table 2. Figure 1a shows a PLUTO drawing of **3d**, and the Newman projection along the C(2)-C(3) axis in figure 1b clearly shows the *trans* geometry of the dialkylamino- and carboxylate groups. The obtained structural parameters are in agreement with those of other simple β-lactams for which X-ray data are available.[15]

Table 2 : Selected Bond Lengths Å and Angles °(with esd's)

C1 -O1	1.213(1)	O1 -C1 -N1	132.3(1)
C1 -N1	1.356(2)	O1 -C1 -C3	134.8(8)
C1 -C3	1.545(2)	N1 -C1 -C3	92.9(1)
N1 -C2	1.464(1)	C1 -N1 -C2	96.3(1)
N1 -C4	1.474(2)	C1 -N1 -C4	131.6(1)
C2 -C3	1.603(2)	C2 -N1 -C4	130.8(8)
C2 -C8	1.502(2)	N1 -C2 -C3	96.6(1)
C3 -N2	1.424(2)	C2 -C3 -C1	83.8(1)

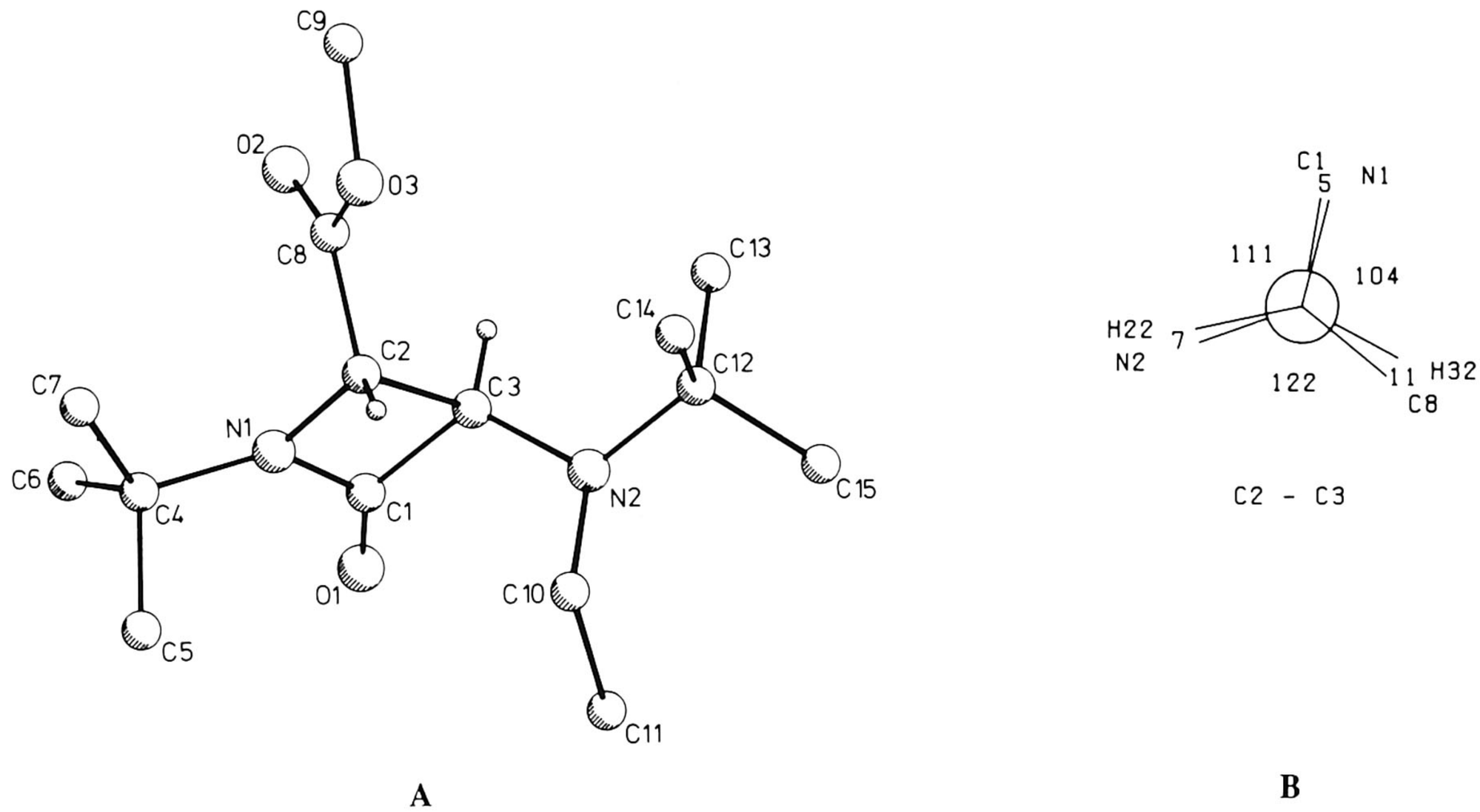


Fig. 1 A: PLUTO drawing of **3d** *with the adopted numbering scheme of the molecule.B: Newman projection along C2-C3.*

It is obvious that the ethyl group present on the amino nitrogen atom of **3d** and the other β-lactams (**1d,2d** and **4d**) must originate from diethylzinc. Therefore, we propose that after the formation of the σ-N, σ-O-$ZnEt_2$ (iminoester) precursor complexes **1b-4b**, migration of an ethyl group from zinc to nitrogen occurs to afford the intermediates **1c-4c** depicted in scheme 1. These intermediates can be described as organozinc enolates of dialkylaminoacid esters. Compounds of this type have been isolated and a crystal structure has been determined for the product obtained from the reaction of t-Bu-N=C(H)C(Me)=O with diethylzinc.[5]

Table : 1 Fractional Positional and Thermal Parameters (with esd's)

Atom	x	y	z	Ueq(*100)
C1	0.7427(2)	0.23842(9)	-0.0876(2)	4.01(9)
C2	0.8438(2)	0.24187(9)	0.1455(2)	4.06(9)
C3	0.7417(2)	0.29576(9)	0.0278(2)	3.88(8)
C4	0.8841(2)	0.12405(9)	0.0099(2)	4.75(9)
C5	0.9954(3)	0.1382(2)	-0.0556(3)	9.6(2)
C6	0.7742(3)	0.0744(1)	-0.0857(4)	12.0(2)
C7	0.9529(3)	0.0946(1)	0.1662(3)	7.6(1)
C8	0.7897(2)	0.2161(1)	0.2628(2)	5.2(1)
C9	0.8213(3)	0.2225(2)	0.5204(3)	9.7(2)
C10	0.9079(2)	0.3698(1)	-0.0303(2)	5.5(1)
C11	0.8831(2)	0.3910(1)	-0.1903(3)	7.3(1)
C12	0.7619(2)	0.4229(1)	0.1045(2)	5.4(1)
C13	0.6193(2)	0.4161(1)	0.1150(3)	6.9(1)
C14	0.8705(3)	0.4192(1)	0.2621(3)	8.6(2)
C15	0.7669(3)	0.4952(1)	0.0331(3)	7.9(2)
N1	0.8197(1)	0.19292(7)	0.0196(1)	4.03(7)
N2	0.7804(1)	0.36622(7)	0.0041(2)	4.34(8)
O1	0.6947(1)	0.23402(7)	-0.2228(1)	5.30(7)
O2	0.6876(2)	0.1817(1)	0.2400(2)	9.6(1)
O3	0.8693(2)	0.23900(8)	0.3978(1)	6.74(9)

We postulate that the intermediates **1c-4c**, in a very fast subsequent reaction, then react either with precursor complex **1b-4b** or with the free α-iminoester **1a-4a** which is in equilibrium with the σ-N,σ-O-$ZnEt_2$-(iminoester) complex. The first step in this reaction is likely to be C-C bond formation between the α-carbon atom of the enolate moiety and the imine carbon atom of the imine unit in an aldol-like condensation reaction. Finally, the β-lactams would be formed through a ring closure with elimination of ethylzinc alkoxide. A similar type of reaction sequence has been postulated for the Reformatsky reaction with benzalaniline, giving β-lactams.[16,17]

Although according to the stoichiometry of the reaction only half an equivalent of diethylzinc is consumed in the formation of one equivalent of the β-lactams **1d-4d**, it appeared to be necessary to carry out the reaction in a 1:1

molar ratio. (When the reaction is carried out with half an equivalent of diethylzinc a β-lactam yield of lower then 50% is obtained.). The most likely explanation for this is that the alkylzinc alkoxide formed in the reaction combines with diethylzinc to produce a mixed aggregate which is inactive in the formation of β-lactams.

Further experiments showed that reaction of a 1:1 mixture of **3a** and **4a** with diethylzinc produces all four possible *trans*-β-lactams in a statistical 1:1:1:1 molar ratio.[13] Furthermore, reaction of alkylzinc halides or diethylzinc in the presence of zinc halides with α-iminoesters leads to the exclusive formation of carbon alkylated products.[18,20] It thus appears that the specific properties of diethylzinc are very important in determining that *trans*-β-lactams are selectively formed from the α-iminoesters. To our knowledge this relatively simple reaction is unique and further studies regarding its mechanism and synthetic scope are being carried out. Results of these investigations will be the subject of forthcoming papers.

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9. A complex of this type with dimethylzinc and α-iminoester **1a** has been isolated and studied ; *M.R.P. van Vliet, G. van Koten, J.F. Modder, J.A.M. van Beek, W. Klaver K. Goubitz* and *C.H. Stam*, J. Organometal. Chem., in press.
10. Compound **1d**: ^{1}H NMR: δ 1.08 (s, 9H, $C(C\underline{H}_3)_3$, 1.31 (s, 9H, $C(C\underline{H}_3)_3$, 1.11 (t, 3H, $N\text{-}CH_2C\underline{H}_3$, 2.48 and 2.74 (m, m, 1H, 1H, $NC\underline{H}_2CH_3$), 1.28 (t, 3H, $OCH_2C\underline{H}_3$), 4.23 (q, 2H, $OC\underline{H}_2CH_3$), 3.95 (d, 1H, NCH-C$\underline{H}$COO, $^3J_{HH}$ 1.6 Hz). 4.38 (d, 1H, NC$\underline{H}$-CHOO, $^3J_{HH}$ 1.6 Hz)
Compound **2d**: ^{1}H NMR: d 0.95 (m, 6H, $CH(C\underline{H}_3)_2$), 1.15 (m, 6H, $CH(C\underline{H}_3)_2$), 3.03 (m, 1H, $C\underline{H}(CH_3)_2$), 3.82 (m, 1H, $C\underline{H}(CH_3)_2$), 1.03 (t, 3H, $NCH_2C\underline{H}_3$), 2.56 (m, 2H, $NC\underline{H}_2CH_3$), 1.24 (t, 3H, $OCH_2C\underline{H}_3$), 4.19 (q, 2H, $OC\underline{H}_2CH_3$), 3.99 (d, 1H, NCH-C$\underline{H}$COO, $^3J_{HH}$ 1.7 Hz, 4.23 (d, 1H, NC$\underline{H}$-CHCOO, $^3J_{HH}$ 1.7 Hz;
Compound **3d**: ^{1}H NMR: d 1.07 (s, 9H, $C(C\underline{H}_3)_3$), 1.31 (s, 9H, $C(C\underline{H}_3)_3$), 1.11 (t, 3H, $NCH_2C\underline{H}_3$), 2.47 and 2.74 (m, m, 1H, 1H, $NC\underline{H}_2CH_3$), 3.76 (s, 3H, OCH_3), 3.97 (d, 1H, NCH-C$\underline{H}$COO, $^3J_{HH}$ 1.6 Hz), 4.38 (d, 1H, NC$\underline{H}$-CHCOO, $^3J_{HH}$ 1.6 Hz);
Compound **4d:** ^{1}H NMR: d 0.96 (m, 6H, $CH(C\underline{H}_3)_2$), 1.14 (m, 6H, $CH(C\underline{H}_3)_2$), 3.00 (,. 1H, $C\underline{H}(CH_3)_2$), 3.85 (m, 1H, $C\underline{H}(CH_3)_2$), 1.02 (t, 3H, $NCH_2C\underline{H}_3$), 2.55 (m, 2H, $NC\underline{H}_2CH_3$), 3.75 (s, 3H, $OC\underline{H}_3$), 4.01 (d, 1H, NCH-C$\underline{H}$COO, $^3J_{HH}$ 1.6 Hz), 4.20 (d, 1H, NC$\underline{H}$-CHCOO, $^3J_{HH}$ 1.6 Hz.)
11a. A value of about 2 Hz for $^3J_{HH}$ is typical for *trans*-β-lactams, for *cis*-β-lactams this value is about 6 Hz. See for example ref. 11b.
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12. Anal. Found (calcd.). Compound **1d**: $C_{16}H_{30}N_2O_3$, m.p. 65-66.5 °C, C 64.33 (64.43), H 9.98 (10.07), N 9.41 (9.40), O 16.36 (16.11); Compound **3d**: $C_{15}H_{28}N_2O_3$, m.p. 25 °C, C 62.32 (63.38), H 9.78 (9.86), N 9.54 (9.86).
13. After work up of the reaction mixture the 250 MHz ^{1}H NMR spectrum of this mixture in C_6D_6 showed four different NC$\underline{H}$-CHCOO resonances in a 1:1:1:1 ratio, from which those of **3d** and **4d** could be assigned by direct comparison with data from authentic samples.
14a. Crystals of the title compound $C_{15}H_{28}N_2O_3$ are monoclinic, space group $P2_1/n$ with cell parameters a = 10.378(2), b = 18.778(2), c = 9.565(1) Å and β = 110.77°(2). Intensity data were collected on a Nonius-CAD4 diffractometer using graphite monochromated MoK_α radiation. The structure was solved using the direct method program package SIMPEL 83 [14b]. Block-diagonal least-squares refinement, anisotropic for C, N, O and isotropic for H converged at R = 0.042 (R_w = 0.057) for 2389 reflections (I > 2.5 σ_I). A weighting scheme $\omega = 1/(5.1 + F_o + .007\ F_o^2)$ and an extinction correction were employed.
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