Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Hydrated forms of *N*-[(3*R*)-3-(4-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl)-2-methylenebutanoyl]-(1*S*,2*R*)-bornane-10,2-sultam and its enantiomer[1]

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Received 17 May 2006
Accepted 24 May 2006
Online 14 July 2006

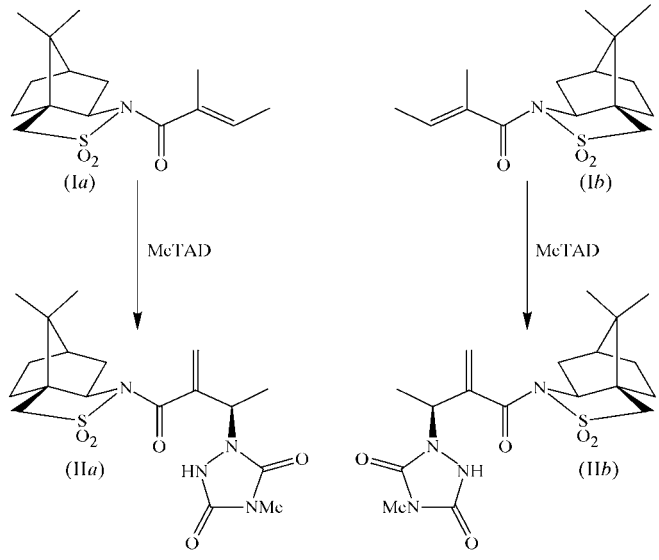
Triazolidinediones react with each enantiomeric bornanesultam derivative of tiglic acid to produce the appropriate ene adduct in high yield and with excellent regioselectivity and diastereoselectivity. The optically pure products, *viz*. *N*-[(3*R*)-3-(4-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl)-2-methylenebutanoyl]-(1*S*,2*R*)-bornane-10,2-sultam 0.15-hydrate, $C_{18}H_{26}N_4O_5S\cdot 0.15H_2O$, and its enantiomer *N*-[(3*S*)-3-(4-methyl-3,5-dioxo-1,2,4-triazolidin-1-yl)-2-methylenebutanoyl]-(1*R*,2*S*)-bornane-10,2-sultam 0.35-hydrate, $C_{18}H_{26}N_4O_5S\cdot 0.35H_2O$, have been characterized by spectroscopy and single-crystal X-ray analysis. Their structures are the result of C*β*-*re* attack of the enophile on the double bond of the alkene.

Comment

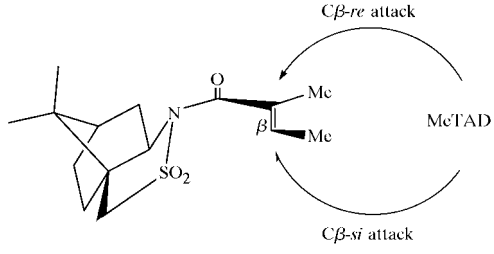
The ene reaction of a triazolidinedione (TAD), singlet oxygen ($^1O_2$) and nitrosoarene with alkenes bearing allylic H atoms has attracted much attention from both the synthetic and the mechanistic points of view, and has recently been reviewed (Vougioukalakis & Orfanopoulos, 2005; Adam & Krebs, 2003). Isotope effect studies suggest that the reaction proceeds in steps through three-membered-ring intermediates, namely a perepoxide, a diaziridinium imide and an aziridine *N*-oxide (Adam, Krebs *et al.*, 2002). The proposal, based on computational results, that there is a biradical intermediate (Singleton & Hang, 1999) has subsequently been challenged by stereochemical and stereoisotopic studies (Stratakis *et al.*, 2001; Vassilikogiannakis *et al.*, 2000).

Stereoselective ene reactions employing chiral auxiliaries have been also reported. Asymmetric ene reactions of singlet oxygen, *N*-phenyltriazolidinedione and nitrosoarene with tigloyl amides bearing the (1*S*,2*R*)-antipode of bornane-10,2-sultam as the chiral auxiliary exhibited high chemical yields and excellent diastereoselectivities (Adam *et al.*, 1998). The configurational assignment of the newly formed stereogenic centers in the major products was made by chemical correlation of their structures with those of known compounds, after removal of the chiral auxiliary moiety. The enantiomerically pure acrylic acid derivatives thus obtained are attractive compounds in the synthesis of *α*-methylene-*β*-amino acids; these substances and, more especially, the peptides derived from them are of biological and pharmaceutical interest.

We have been involved in the development of such stereoselective ene reactions for some time and now communicate our results. These include the X-ray structures of (II*a*) and (II*b*), the enantiomeric ene adducts of *N*-methyltriazolidinedione, MeTAD, obtained from its reaction with the two chiral tigloyl amides (I*a*) and (I*b*), each of which bears an antipode of bornanesultam. The reactions between (I) and PhTAD are analogous to those shown in the first scheme below.



The structures of the two MeTAD adducts (Fig. 1) establish that the stereochemical outcome of the reaction is consistent with the proposed *π*-facially diastereoselective enophilic



attack of MeTAD on the tiglic acid derivative (I) (Adam, Degen *et al.*, 2002). Thus, starting with the chiral tiglate (I*a*) as the alkene, the major ene product (II*a*), obtained by column chromatography and subsequent crystallization, was found to have a newly formed stereogenic centre with an *R* configuration, whereas the ene product (II*b*) from the (I*b*) tiglate amide had an *S* configuration at the new stereogenic centre.

[1] Part of this work was presented as a poster at the 13th International Conference on Organic Synthesis (ICOS-13), Warsaw, Poland, July 1–5, 2000; Y. Elemes: Highly Diastereoselective Ene Reactions with the Aid of a Chiral Auxiliary, p. 265.

  DOI: 10.1107/S0108270106019524

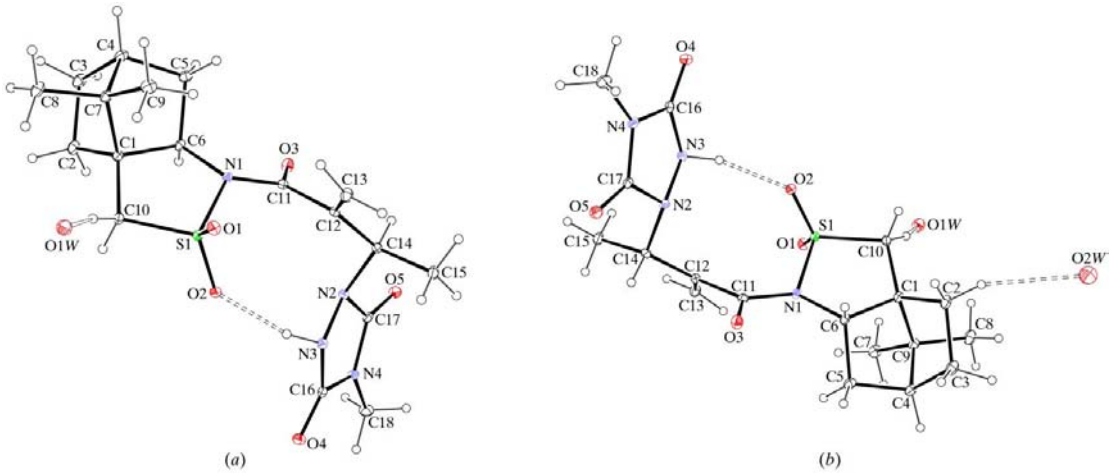


Figure 1
The structures of MeTAD adducts (*a*) (II*a*) and (*b*) (II*b*). The X-ray experiment indicates that the respective configurations at C1, C4, C6 and C14 are *SRRR* in (II*a*) and *RSSS* in (II*b*). Hydrogen bonds are indicated by broken lines and 20% probability displacement ellipsoids are shown.

Adam, Degen *et al.* (2002) have argued that electrostatic repulsion between the sulfonyl and carbonyl groups, and steric interaction between the bornane skeleton and the alkene substituents, give (I), the well defined *s-trans* conformation shown in the scheme above. Repulsions between the sulfonyl group and the incoming enophile then favour Cβ-*re* attack on the double bond of the alkene over Cβ-*si* attack. In addition, the products (II) contain intramolecular N3—H$\cdots$O2 hydrogen bonds (Fig. 1, and Tables 1 and 2); this source of thermodynamic stability may not be available to the products of Cβ-*si* attack, in which the positions of the H and MeTAD substituents at C14 would be interchanged.

The X-ray analyses of (II*a*) and (II*b*) at 100 K give experimental absolute configurations consistent with conservation of configuration at the stereogenic centres in the starting tiglate amides (I*a*) and (I*b*). Apart from minor differences involving partially occupied solvent water sites (see below), the two crystal structures are mirror images. Corresponding bond distances and angles agree well and fully support the formulations in the first scheme. The final difference maps are featureless. The X-ray analyses therefore indicate that the samples are optically pure. As we have recently observed in the case of a fenchone derivative (Fraile *et al.*, 2003), crystallization in a space group such as $P4_12_12$, which has only pure rotational symmetry, is not in itself a guarantee of optical purity.

In both (II*a*) and (II*b*), there are sites on diad axes thought to be partially occupied by water O atoms. The associated H atoms were not located. In (II*a*), there is one such site; its contacts [O1*W*$\cdots$H10*B* = 2.27 Å and O1*W*$\cdots$O3($-\frac{1}{2}+y, \frac{3}{2}-x, \frac{1}{4}+z$) = 2.841 (4) Å] are consistent with atom O1*W* donating two and accepting two hydrogen bonds. In (II*b*), there are two such sites. Atom O1*W* has a similar environment to the corresponding site in (II*a*) but has a higher occupancy. Atom O2*W* makes O2*W*$\cdots$H2*A* (2.53 Å) and O2*W*$\cdots$O4($x-1, y, z$) [2.995 (11) Å] contacts, and has very low occupancy. The presence of two hydrate sites and the higher overall water content of (II*b*) may explain the slightly greater length of its *c* axis.

The atomic U^{ij} values of the main residues are moderately well reproduced by **TLS** analyses [$R2 = (\Sigma\Delta U^2/\Sigma U^2)^{1/2}$ = 0.173 and 0.170; Schomaker & Trueblood, 1968]. The worst discrepancy in the Hirshfeld (1976) rigid bond test is ΔU = 0.004 (1_1) Å^2 for C1—C10 in (II*b*).

Experimental

The optically pure tiglic amides (I) were synthesized in high yield according to published procedures (Oppolzer *et al.*, 1988, and references therein) and recrystallized from methanol. The ene reactions were performed in dry CH_2Cl_2 at room temperature. After 24 h, the original pink colour of the solution had disappeared. The solvent was removed, first in a rotary evaporator and then with a high vacuum pump. The remaining material was chromatographed on an SiO_2 column (eluant: EtOAc/*n*-hexane, 1/3 *v*/*v*). The ^{1}H NMR spectra of the product showed a diastereomeric ratio of *ca* 95:5 (the same ratio was observed when PhTAD was the enophile). After fractional recrystallization of the crude mixture, it was evident from the ^{1}H NMR spectra that only the major diastereomer (II) had been isolated. The pure stereoisomers (II) were characterized by ^{1}H NMR, ^{13}C NMR and FT–IR spectroscopy, elemental analysis, and ESI and FAB mass spectrometry. Their optical rotations were also measured; each pair of enantiomeric products showed rotations of nearly identical magnitudes but of opposite signs. For (II*a*), 100 mg of (I*a*) gave (II*a*) in 60% yield (83 mg) after crystallization (EtOAc/*n*-hexane), $[\alpha]_D = -133.8^\circ$ (*c* = 0.12, CH_2Cl_2, 290 K). FT–IR (KBr, cm^{-1}): ν 3245.1, 2988.4, 1774.4, 1710.3, 1686.0, 1467.3, 1420.8, 1340.4, 1321.1, 1288.7, 1130.6, 973.6, 771.5, 536.6; ^{1}H NMR ($CDCl_3$, 250 MHz): δ 1.01 (*s*, 3H, CH_3), 1.23 (*s*, 3H, CH_3), 1.32–1.44 (*m*, 2H, CH_2), 1.35 (*d*, *J* = 6.75 Hz, 3H, CH_3), 1.63 (*s*, 3H, CH_3), 1.80–2.10 (*m*, 5H, CH, 2 × CH_2), 3.05 (*s*, 3H, CH_3), 3.43 (*d*, *J* = 13.76 Hz, 1H, CH), 3.57 (*d*, *J* = 13.76 Hz, 1H, CH), 4.09 (*dd*, *J* = 5.00 and 7.25 Hz, 1H, CH), 5.36 (*tq*, *J* = 1.58 and 6.75 Hz, 1H, CH), 5.96 (*dd*, *J* = 0.92 and 1.72 Hz, 1H, CH, olefinic), 6.19 (*dd*, *J* = 0.92 and 1.44 Hz, 1H, CH, olefinic), 7.51 (*s*, *br*, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ 13.2, 19.8, 21.4, 25.2, 26.2, 33.2, 38.3, 45.2, 47.7, 48.0, 52.4, 53.6, 66.1, 127.8, 141.1, 155.1, 155.7, 168.4. Analysis calculated for $C_{18}H_{26}N_4O_5S$: C 52.67, H 6.38, N 13.65, S 7.81%; found: C 52.65, H 6.37, N 13.64, S 7.79%; FAB–MS: calculated for $C_{18}H_{26}N_4O_5S$ [*M*] = 410.49; found = 411 (100). For (II*b*), 100 mg of (I*b*) gave (II*b*) in 63% yield (87 mg)

after crystallization (EtOAc/*n*-hexane), $[\alpha]_D$ = +133.1° (*c* = 0.09, CH_2Cl_2, 291 K). Analysis calculated for $C_{18}H_{26}N_4O_5S$: C 52.67, H 6.38, N 13.65, S 7.81%; found: C 52.66, H 6.36, N 13.64, S 7.78%; FAB–MS: calculated for $C_{18}H_{26}N_4O_5S$ [*M*] = 410.49; found = 411 (100).

Compound (II*a*)

Crystal data

$C_{18}H_{26}N_4O_5S{\cdot}0.151H_2O$
M_r = 413.21
Tetragonal, $P4_32_12$
a = 12.2857 (1) Å
c = 26.1898 (2) Å
V = 3953.05 (5) Å^3
Z = 8
D_x = 1.388 Mg m^{-3}
Mo *K*α radiation
μ = 0.20 mm^{-1}
T = 100 K
Needle, colourless
0.45 × 0.20 × 0.20 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
9977 measured reflections
5702 independent reflections
5366 reflections with $I > 2\sigma(I)$
R_{int} = 0.016
θ_{max} = 30.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.030
$wR(F^2)$ = 0.077
S = 1.03
5702 reflections
267 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0423P)^2 + 0.932P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.39 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Absolute structure: Flack (1983), 2381 Friedel pairs
Flack parameter: −0.02 (5)

Table 1
Hydrogen-bond geometry (Å, °) for (II*a*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3N···O2	0.935 (17)	1.914 (17)	2.8254 (14)	164.1 (14)

Compound (II*b*)

Crystal data

$C_{18}H_{26}N_4O_5S{\cdot}0.3485H_2O$
M_r = 416.77
Tetragonal, $P4_12_12$
a = 12.2794 (2) Å
c = 26.3417 (5) Å
V = 3971.90 (12) Å^3
Z = 8
D_x = 1.394 Mg m^{-3}
Mo *K*α radiation
μ = 0.20 mm^{-1}
T = 100 K
Needle, colourless
0.34 × 0.24 × 0.24 mm

Data collection

Nonius KappaCCD diffractometer
φ and ω scans
10281 measured reflections
5761 independent reflections
4925 reflections with $I > 2\sigma(I)$
R_{int} = 0.029
θ_{max} = 30.0°

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.094
S = 0.98
5761 reflections
269 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.051P)^2 + 0.6973P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ < 0.001
$\Delta\rho_{max}$ = 0.33 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}
Absolute structure: Flack (1983), 2399 Friedel pairs
Flack parameter: −0.04 (6)

Table 2
Hydrogen-bond geometry (Å, °) for (II*b*).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3N···O2	0.95 (2)	1.91 (2)	2.8263 (18)	161.2 (17)

All C- and N-bonded H atoms were located unambiguously in difference maps. In the final refinement, the positions of C-bonded H atoms were determined by HFIX instructions in *SHELXL97* (Sheldrick, 1997); they were then treated as riding on their parent atoms, with C—H distances of 0.95 (=CH$_2$), 0.98 (CH$_3$), 0.99 (CH$_2$) or 1.00 Å (CH), and U_{iso}(H) values of 1.5 (methyl) or 1.2 times U_{eq}(C). Apart from one CH$_3$ group in (II*b*), an orientation parameter was refined for each methyl group. The H atom bonded to atom N3 was freely refined. The disordered water H atoms were neither located nor included in the calculations.

For both compounds, data collection: *COLLECT* (Nonius, 2000); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997) and *SCALEPACK*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3* (Farrugia, 1997); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

This work was supported (programme No. 667) by the Research Committee of the University of Ioannina, Greece, and by Glasgow University, Scotland. We thank the NMR centres of both the University of Ioannina, Greece, and the Institute of Organic Chemistry, University of Erlangen–Nürnberg, Germany, for the NMR spectra.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: DN3017). Services for accessing these data are described at the back of the journal.

References

Adam, W., Degen, H.-G., Krebs, O. & Saha-Moller, C. R. (2002). *J. Am. Chem. Soc.* **124**, 12938–12939.
Adam, W. & Krebs, O. (2003). *Chem. Rev.* **103**, 4131–4146.
Adam, W., Krebs, O., Orfanopoulos, M., Stratakis, M. & Vougioukalakis, G. C. (2002). *J. Org. Chem.* **68**, 2420–2425.
Adam, W., Wirth, T., Pastor, A. & Peters, K. (1998). *Eur. J. Org. Chem.* pp. 501–506.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Farrugia, L. J. (1999). *J. Appl. Cryst.* **32**, 837–838.
Flack, H. D. (1983). *Acta Cryst.* A**39**, 876–881.
Fraile, A. G., Morris, D. G., Martinez, A. G., de la Moya Cerereo, S., Muir, K. W., Ryder, K. S. & Vilar, E. T. (2003). *Org. Biomol. Chem.* **1**, 700–704.
Hirshfeld, F. L. (1976). *Acta Cryst.* A**32**, 239–244.
Nonius (2000). *COLLECT*. Nonius BV, Delft, The Netherlands.
Oppolzer, W., Poli, G., Starkemann, C. & Bernardinelli, G. (1988). *Tetrahedron Lett.* **29**, 3559–3562.
Otwinowski, Z. & Minor, W. (1997). *Methods in Enzymology*, Vol. 276, *Macromolecular Crystallography*, Part A, edited by C. W. Carter Jr & R. M. Sweet, pp. 307–326. New York: Academic Press.
Schomaker, V. & Trueblood, K. N. (1968). *Acta Cryst.* B**24**, 63–76.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Singleton, D. A. & Hang, C. (1999). *J. Am. Chem. Soc.* **121**, 11885–11893.
Stratakis, M., Hatzimarinaki, M., Froudakis, G. E. & Orfanopoulos, M. (2001). *J. Org. Chem.* **66**, 3682–3687.
Vassilikogiannakis, G., Elemes, Y. & Orfanopoulos, M. (2000). *J. Am. Chem. Soc.* **122**, 9540–9541.
Vougioukalakis, G. C. & Orfanopoulos, M. (2005). *Synlett*, pp. 713–731.