

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 enantiomer¹

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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, C₁₈H₂₆N₄O₅S·0.15H₂O, 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, C₁₈H₂₆N₄O₅S·0.35H₂O, have been characterized by spectroscopy and single-crystal X-ray analysis. Their structures are the result of *Cβ-re* attack of the enophile on the double bond of the alkene.

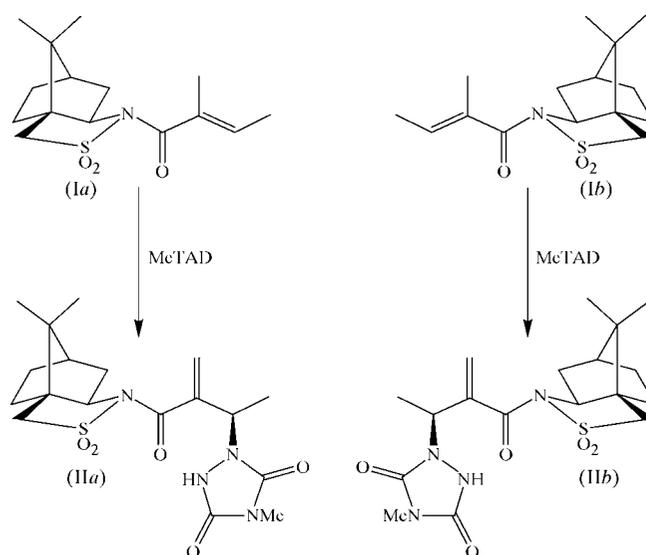
Comment

The ene reaction of a triazolidinedione (TAD), singlet oxygen (¹O₂) 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).

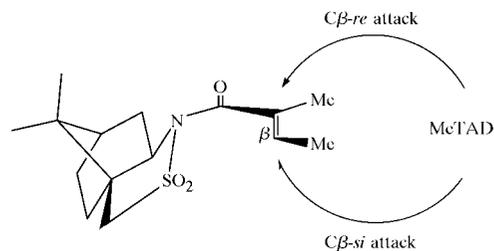
Stereoselective ene reactions employing chiral auxiliaries have been also reported. Asymmetric ene reactions of singlet oxygen, *N*-phenyltriazolidinedione and nitrosoarene with

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.

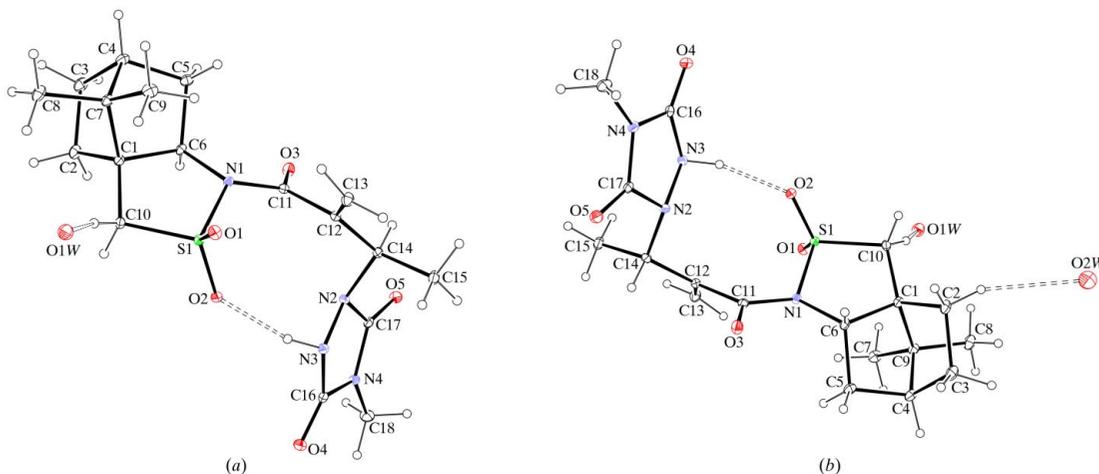


Figure 1

The structures of MeTAD adducts (a) (IIa) and (b) (IIb). The X-ray experiment indicates that the respective configurations at C1, C4, C6 and C14 are *SRRR* in (IIa) and *RSSS* in (IIb). 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 *C β -re* attack on the double bond of the alkene over *C β -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 *C β -si* attack, in which the positions of the H and MeTAD substituents at C14 would be interchanged.

The X-ray analyses of (IIa) and (IIb) at 100 K give experimental absolute configurations consistent with conservation of configuration at the stereogenic centres in the starting tiglate amides (Ia) and (Ib). 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 *P4₁2₁2*, which has only pure rotational symmetry, is not in itself a guarantee of optical purity.

In both (IIa) and (IIb), there are sites on diad axes thought to be partially occupied by water O atoms. The associated H atoms were not located. In (IIa), there is one such site; its contacts [O1W \cdots H10B = 2.27 Å and O1W \cdots O3($-\frac{1}{2} + y, \frac{3}{2} - x, \frac{1}{4} + z$) = 2.841 (4) Å] are consistent with atom O1W donating two and accepting two hydrogen bonds. In (IIb), there are two such sites. Atom O1W has a similar environment to the corresponding site in (IIa) but has a higher occupancy. Atom O2W makes O2W \cdots H2A (2.53 Å) and O2W \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 (IIb) 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 [$R2 = (\sum \Delta U^2 / \sum U^2)^{1/2} = 0.173$ and 0.170 ; Schomaker & Trueblood, 1968]. The worst discrepancy in the Hirshfeld (1976) rigid bond test is $\Delta U = 0.004$ (1_1) Å² for C1—C10 in (IIb).

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 CH₂Cl₂ 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 SiO₂ column (eluant: EtOAc/*n*-hexane, 1/3 *v/v*). The ¹H 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 ¹H NMR spectra that only the major diastereomer (II) had been isolated. The pure stereoisomers (II) were characterized by ¹H NMR, ¹³C 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 (IIa), 100 mg of (Ia) gave (IIa) in 60% yield (83 mg) after crystallization (EtOAc/*n*-hexane), $[\alpha]_D = -133.8^\circ$ ($c = 0.12$, CH₂Cl₂, 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; ¹H NMR (CDCl₃, 250 MHz): δ 1.01 (*s*, 3H, CH₃), 1.23 (*s*, 3H, CH₃), 1.32–1.44 (*m*, 2H, CH₂), 1.35 (*d*, $J = 6.75$ Hz, 3H, CH₃), 1.63 (*s*, 3H, CH₃), 1.80–2.10 (*m*, 5H, CH, 2 \times CH₂), 3.05 (*s*, 3H, CH₃), 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 (*tg*, $J = 1.58$ 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); ¹³C NMR (CDCl₃, 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 C₁₈H₂₆N₄O₅S: 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 C₁₈H₂₆N₄O₅S [*M*] = 410.49; found = 411 (100). For (IIb), 100 mg of (Ib) gave (IIb) in 63% yield (87 mg)

after crystallization (EtOAc/*n*-hexane), $[\alpha]_D = +133.1^\circ$ ($c = 0.09$, CH₂Cl₂, 291 K). Analysis calculated for C₁₈H₂₆N₄O₅S: 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 C₁₈H₂₆N₄O₅S $[M] = 410.49$; found = 411 (100).

Compound (IIa)

Crystal data

C₁₈H₂₆N₄O₅S·0.151H₂O $D_x = 1.388$ Mg m⁻³
 $M_r = 413.21$ Mo $K\alpha$ radiation
 Tetragonal, $P4_32_12$ $\mu = 0.20$ mm⁻¹
 $a = 12.2857$ (1) Å $T = 100$ K
 $c = 26.1898$ (2) Å Needle, colourless
 $V = 3953.05$ (5) Å³ $0.45 \times 0.20 \times 0.20$ mm
 $Z = 8$

Data collection

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

Refinement

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

Table 1

Hydrogen-bond geometry (Å, °) for (IIa).

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|--------------------|------------|-------------|-------------|---------------|
| N3—H3N \cdots O2 | 0.935 (17) | 1.914 (17) | 2.8254 (14) | 164.1 (14) |

Compound (IIb)

Crystal data

C₁₈H₂₆N₄O₅S·0.3485H₂O $D_x = 1.394$ Mg m⁻³
 $M_r = 416.77$ Mo $K\alpha$ radiation
 Tetragonal, $P4_12_12$ $\mu = 0.20$ mm⁻¹
 $a = 12.2794$ (2) Å $T = 100$ K
 $c = 26.3417$ (5) Å Needle, colourless
 $V = 3971.90$ (12) Å³ $0.34 \times 0.24 \times 0.24$ mm
 $Z = 8$

Data collection

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

Refinement

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

Table 2

Hydrogen-bond geometry (Å, °) for (IIb).

| $D-H\cdots A$ | $D-H$ | $H\cdots A$ | $D\cdots A$ | $D-H\cdots A$ |
|--------------------|----------|-------------|-------------|---------------|
| N3—H3N \cdots 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 (=CH₂), 0.98 (CH₃), 0.99 (CH₂) or 1.00 Å (CH), and $U_{iso}(H)$ values of 1.5 (methyl) or 1.2 times $U_{eq}(C)$. Apart from one CH₃ group in (IIb), 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).

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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.* **A39**, 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.* **A32**, 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.* **B24**, 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.