$C_{46}H_{70}N_4O_{12}$

Frenz, B. A. (1985). *Enraf–Nonius SDP-Plus Structure Determination Package*. Version 3.0. Enraf–Nonius, Delft, The Netherlands.

Miller, J. S. & Epstein, A. J. (1994). *Angew. Chem.* **106**, 399.

North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A24, 351–359.

Rassat, A. (1990). *Pure Appl. Chem.* **62**, 223–227.

Seff, K. (1972). *Acta Cryst.* B28, 2298–2301.

Sheldrick, G. M. (1990). *Acta Cryst.* A46, 467–473.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.

Sholle, V. D., Prokop'ev, A. I., Sortova, K. A., Sarymsakov, Sh. S. & Rozantev, E. G. (1981). *Izv. Akad. Nauk SSSR Ser. Khim.* 11, 2578–2583.

Spek, A. L. (1993). *PLUTON93. Program for the Display and Analysis of Crystal and Molecular Structures*. University of Utrecht, The Netherlands.

Stoe & Cie (1991). *REDU4. Data Reduction Program*. Version 7.08. Stoe & Cie, Darmstadt, Germany.

Unique *trans-syn-cis* [6.6.7] Tricycle Derivative from Transannular Diels–Alder Contraction of a Model 15-Membered *trans-cis-cis* Macrocyclic Triene

Marc Drouin,[a] Dennis G. Hall,[b] Alain-Sébastien Caillé[b] and Pierre Deslongchamps[b]

[a]*Laboratoire de Diffraction des Rayons-X, Département de Chimie, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1, and [b]Laboratoire de Synthèse Organique, Département de Chimie, Faculté des Sciences, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1. E-mail: marc.drouin@courrier.usherb.ca*

Abstract

A model 15-membered *trans-cis-cis* macrocyclic triene, (*trans-cis-cis*)-tetramethyl (4E,11Z,13E)-5-formylcyclopentadeca-4,11,13-triene-1,1,8,8-tetracarboxylate, $C_{24}H_{32}O_9$, was synthesized and led to the exclusive formation of a *trans-syn-cis* [6.6.7] tricyclic compound upon a transannular Diels–Alder reaction. The structure of the precursor and a p-bromobenzoyl analog of the product, (*trans-syn-cis*)-tetramethyl *rac*-(1S,2S,7R,10R)-(8Z)-1-(4-bromobenzoyloxymethyl)tricyclo[8.5.0.0^{2,7}]pentadec-8-ene-5,5,13,13-tetracarboxylate ethanol solvate, $3C_{31}H_{37}BrO_{10}\cdot0.76C_2H_6O$, were determined in order to establish their exact geometries and ring-junction stereochemistries.

Comment

The power of the transannular Diels–Alder (TADA) reaction of 15-membered macrocyclic trienes for the

stereoselective generation of an *ABC* [6.6.7] tricyclic steroid skeleton in a single chemical step has recently been demonstrated (Hall, Müller & Deslongchamps, 1995a,b). We reported thereafter the crystal structure of such a condensed ring structure with *trans-anti-cis* (TAC) ring-junction stereochemistry (Michel, Drouin & Hall, 1995). This structure was the result of a facile cycloaddition on a *trans-trans-trans*-cyclopentadecatriene. We now report the crystal structure of a novel *trans-syn-cis* (TSC) *ABC* [6.6.7] tricycle, (2), related to the important bioactive natural products aphidicolin (Dalziel, Hesp, Stevenson & Jarvis, 1973) and the scopadulan family (Hayashi *et al.*, 1987).

$E = CO_2CH_3$

(2′′) R = CHO
(2) R = CH$_2$O-p-bromobenzoate
(X-ray)
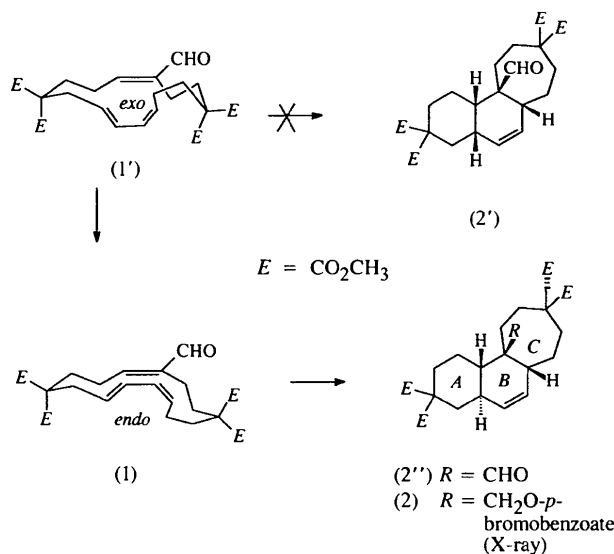
The tricyclic adduct (2) derives from a stereospecific Lewis acid-catalyzed TADA reaction of the formyl-substituted *trans-cis-cis* (TCC) cyclopentadecatriene (1) (Hall *et al.*, 1995). In order for (1) to collapse into compound (2′), the *trans-cis* diene moiety of (1) would have to adopt the unfavorable *cisoid* form characterized by strong allylic interactions of the internal methylene (1′). In such a form, the macrocycle may react through an *exo* approach leading to a highly strained transition-state structure having a *trans*-diaxial ring junction between incipient ring B in a boat conformation and the seven-membered ring C. Consequently, the corresponding *cis-syn-trans* tricyclic adduct (2′) is not actually observed. Alternatively, the *endo* approach is freed of any particular ring strain or non-bonded interactions. Hence, after the TADA reaction, the corresponding TSC tricycle (2′′) is obtained exclusively. Its p-bromobenzoyl derivative, (2), as well as the parent cyclopentadecatriene, (1), could be crystallized and the ensuing X-ray diffraction analysis established their structures.

ORTEP (Johnson, 1995) perspective views of the macrocycle (1) and the tricyclic adduct (2) (three in-

dependent molecules) which establish their predicted stereochemistry are shown in Fig. 1. Compound (1) was easily crystallized. Its crystal structure displays TCC geometry of the fifteen-membered macrocycle. It adopts an extended conformation with a *transoid* diene

in a slightly strained conformation. This results in a partially broken conjugated system [C10—C11—C12—C13 166.8 (4)°]. The crystallization of compound (2″) was not possible; therefore, it was converted into its corresponding *p*-bromobenzoate derivative, (2). This com-
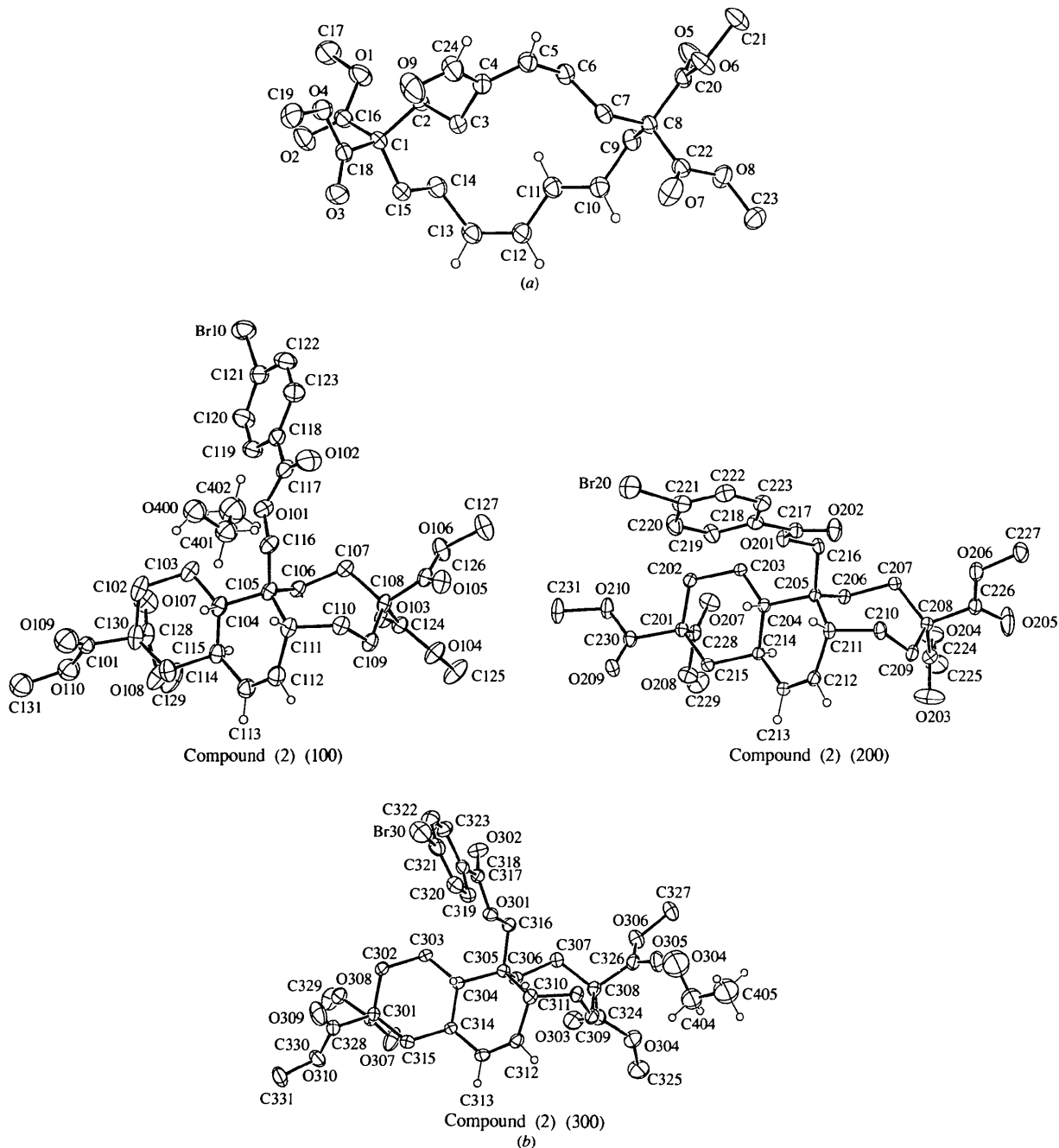

Compound (2) (100)

Compound (2) (200)

Compound (2) (300)

(*b*)

Fig. 1. *ORTEP* (Johnson, 1995) perspective views of (*a*) (1) and (*b*) the three independent molecules of (2), showing the labelling of the non-H atoms. The two orientations of the ethanol molecule are presented, one with 100 and one with 300. Only one orientation for the disordered ester group is shown. For all views, displacement ellipsoids are drawn at the 30% probability level, H atoms have been omitted for clarity, except for those on *sp²*-C atoms and those on ring junctions, which are drawn as small circles of arbitrary radii.

pound was also difficult to crystallize and the resulting crystal packing is rather complex. It is interesting to note that ring *B* adopts a chair conformation, in contrast to the required boat conformation initially formed upon cycloaddition (Lamothe, Ndibwami & Deslongchamps, 1988*a,b*). In order to pack, (2) must use three different molecules in the asymmetric unit. The molecules are labelled 100, 200 and 300 for differentiation. Each molecule adopts a different conformation for its *p*-bromobenzoate moiety (Table 2). There is also one disordered partially occupied (76%) molecule of ethanol in the asymmetric unit. The occupancy-factor split is 0.30 (1)/0.46 (1). The two orientations are such that hydrogen bonds occur between O400—H400 and O107, and O403—H403 and O305(1 + *x*, *y*, *z*) (Table 3). Enlarged views of the crystal packing (archived as supplementary material) show sandwich-type stacking. Indeed, the 200 molecules form a layer in the center of the cell, distinct from the 100 and 300 molecules. The layers are in the *xy* plane. The 100 molecules stack with their respective *p*-bromobenzoate moieties one over the other. The benzoate group of each 200 molecule is folded over its symmetrically-related stereoisomer in order to minimize contacts with the 100 and 300 molecules. No abnormally short contacts were observed.

Experimental

Details of the synthesis of the two compounds are given by Hall, Caillé, Drouin, Lamothe, Müller & Deslongchamps (1995). Compounds (1) and (2) were crystallized by slow evaporation of an ethanolic solution.

Compound (1)

Crystal data

$C_{24}H_{32}O_9$	Cu $K\alpha$ radiation
$M_r = 464.51$	$\lambda = 1.54184$ Å
Triclinic	Cell parameters from 24
$P\bar{1}$	reflections
$a = 6.9449\,(5)$ Å	$\theta = 30\text{--}40°$
$b = 10.5817\,(5)$ Å	$\mu = 0.81$ mm^{-1}
$c = 17.8569\,(8)$ Å	$T = 293$ K
$\alpha = 74.196\,(4)°$	Prism
$\beta = 78.952\,(4)°$	$0.30 \times 0.10 \times 0.10$ mm
$\gamma = 73.558\,(4)°$	Colorless
$V = 1201.68\,(12)$ Å^3	
$Z = 2$	
$D_x = 1.284$ Mg m^{-3}	
D_m not measured	

Data collection

Nonius CAD-4 diffractom-	$R_{int} = 0.011$
eter	$\theta_{max} = 69.57°$
$\theta/2\theta$ scans	$h = -7 \to 7$
Absorption correction: none	$k = 0 \to 11$
4975 measured reflections	$l = -20 \to 21$
4369 independent reflections	2 standard reflections
3057 reflections with	frequency: 60 min
$I_{net} > 2.5\sigma(I_{net})$	intensity decay: <1%

Refinement

Refinement on F	$\Delta\rho_{max} = 0.22$ e Å^{-3}
$R = 0.046$	$\Delta\rho_{min} = -0.18$ e Å^{-3}
$wR = 0.061$	Extinction correction:
3057 reflections	Larson (1970)
299 parameters	Extinction coefficient:
H atoms not refined	$0.27\,(7) \times 10^{-6}$
$w = 1/[\sigma^2(F) + 0.0008F^2]$	Scattering factors from *Inter-*
$(\Delta/\sigma)_{max} = 0.001$	*national Tables for X-ray*
	Crystallography (Vol. IV)

Table 1. *Selected torsion angles (°) for (1)*

C3—C4—C5—C6	−2.2 (5)	C10—C11—C12—C13	166.8 (4)
C9—C10—C11—C12	174.3 (3)	C11—C12—C13—C14	−6.9 (6)

Compound (2)

Crystal data

$3C_{31}H_{37}BrO_{10}.0.76C_2H_6O$	Cu $K\alpha$ radiation
$M_r = 1983.6$	$\lambda = 1.54184$ Å
Triclinic	Cell parameters from 16
$P\bar{1}$	reflections
$a = 13.549\,(2)$ Å	$\theta = 30\text{--}40°$
$b = 15.413\,(2)$ Å	$\mu = 2.304$ mm^{-1}
$c = 24.490\,(2)$ Å	$T = 293\,(2)$ K
$\alpha = 79.073\,(11)°$	Plate
$\beta = 75.749\,(9)°$	$0.30 \times 0.20 \times 0.07$ mm
$\gamma = 70.254\,(12)°$	Colorless
$V = 4633.8\,(10)$ Å^3	
$Z = 2$	
$D_x = 1.422$ Mg m^{-3}	
D_m not measured	

Data collection

Nonius CAD-4 diffractom-	12 422 reflections with
eter	$I > 2\sigma(I)$
$\theta/2\theta$ scans	$R_{int} = 0.019$
Absorption correction:	$\theta_{max} = 69.81°$
empirical ψ scan based	$h = -15 \to 16$
on 9 azimuthal reflections	$k = 0 \to 18$
(*NRCVAX ABSORP*;	$l = -28 \to 29$
Gabe, Le Page, Charland,	3 standard reflections
Lee & White, 1989)	frequency: 60 min
$T_{min} = 0.782$, $T_{max} = 0.997$	intensity decay: none
26 568 measured reflections	
17 470 independent	
reflections	

Refinement

Refinement on F^2	$\Delta\rho_{max} = 1.064$ e Å^{-3}
$R[F^2 > 2\sigma(F^2)] = 0.061$	$\Delta\rho_{min} = -0.999$ e Å^{-3}
$wR(F^2) = 0.175$	Extinction correction:
$S = 1.067$	*SHELXL93* (Sheldrick,
17 425 reflections	1993)
1160 parameters	Extinction coefficient:
H atoms constrained	0.00014 (5)
$w = 1/[\sigma^2(F_o^2) + (0.0788P)^2$	Scattering factors from
$+ 2.8467P]$	*International Tables for*
where $P = (F_o^2 + 2F_c^2)/3$	*Crystallography* (Vol. C)
$(\Delta/\sigma)_{max} = -0.310$	

Table 2. *Selected torsion angles (°) for (2)*

O101—C117—C118—C123	175.4 (4)
C118—C117—O101—C116	177.6 (3)
C105—C116—O101—C117	−144.6 (3)
C205—C216—O201—C217	116.0 (3)
C216—O201—C217—C218	178.4 (3)
C223—C218—C217—O201	−165.6 (3)
O301—C317—C318—C323	−172.7 (3)
C318—C317—O301—C316	−175.1 (3)
C305—C316—O301—C317	−153.4 (3)

Table 3. *Hydrogen-bonding geometry (Å, °) for (2)*

D—H···A	D—H	H···A	D···A	D—H···A
O400—H400···O107	0.82	2.253	3.023 (19)	156.3
O403—H403···O305^i	0.82	2.175	2.997 (14)	171.5

Symmetry code: (i) $1 + x, y, z$.

For compound (2), the disordered ester was split into two partially occupied groups with 50% occupancy factors. All disordered atoms were refined isotropically. The *SAME* and *SADI* restraints in *SHELXL93* (Sheldrick, 1993) were applied for refinement. The ethanol solvent-occupancy refinement converged to 0.46 (1) and 0.30 (1) for O400—C401—C402 and O403—C404—C405, respectively. A restrain refinement was applied using the *SAME* and *SADI* options. All H atoms were geometrically placed. The O—H and C—H distances were set to 0.82 and 0.93–0.98 Å, respectively. The highest and lowest residual densities for (2) were located in the vicinity of the Br atoms.

For both compounds, data collection: *NRCCAD DATCOL* (Le Page, White & Gabe, 1986); cell refinement: *NRCCAD TRUANG*; data reduction: *NRCVAX DATRD2* (Gabe, Le Page, Charland, Lee & White, 1989). Program(s) used to solve structures: *NRCVAX SOLVER* for (1); *SIR*92 (Altomare, Cascarano, Giacovazzo & Guargliardi, 1993) for (2). Program(s) used to refine structures: *NRCVAX LSTSQ* for (1); *SHELXL93* (Sheldrick, 1993) for (2). For both compounds, molecular graphics: *ORTEP* in *Xtal_GX* (Johnson, 1995). Software used to prepare material for publication: *NRCVAX TABLES* for (1); *SHELXL93 ACTA* for (2).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1245). Services for accessing these data are described at the back of the journal.

References

Altomare, A., Cascarano, G., Giacovazzo, C. & Guagliardi, A. (1993). *J. Appl. Cryst.* **26**, 343–350.

Dalziel, W., Hesp, B., Stevenson, K. M. & Jarvis, J. A. J. (1973). *J. Chem. Soc. Perkin Trans.* 1, pp. 2841–2851.

Gabe, E. J., Le Page, Y., Charland, J.-P., Lee, F. L. & White, P. S. (1989). *J. Appl. Cryst.* **22**, 384–387.

Hall, D. G., Caillé, A.-S., Drouin, M., Lamothe, S., Müller, R. & Deslongchamps, P. (1995). *Synthesis*, **9**, 1081–1087.

Hall, D. G., Müller, R. & Deslongchamps, P. (1995a). *Can. J. Chem.* pp. 1675–1694.

Hall, D. G., Müller, R. & Deslongchamps, P. (1995b). *Can. J. Chem.* pp. 1695–1710.

Hayashi, T., Kishi, M., Kawasaki, M., Arisawa, M., Shimizu, M., Suzuki, S., Yoshizaki, M., Morita, N., Tezuka, Y., Kikuchi, T., Berganza, L. H., Ferro, E. & Balsualdo, I. (1987). *Tetrahedron Lett.* **28**, 3693–3696.

Johnson, C. K. (1995). *ORTEP*. In *Xtal_GX*, edited by S. R. Hall & D. J. du Boulay. University of Western Australia, Australia.

Lamothe, S., Ndibwami, A. & Deslongchamps, P. (1988a). *Tetrahedron Lett.* **29**, 1639–1640.

Lamothe, S., Ndibwami, A. & Deslongchamps, P. (1988b). *Tetrahedron Lett.* **29**, 1641–1644.

Larson, A. C. (1970). *Crystallographic Computing*, edited by F. R. Ahmed, S. R. Hall & C. P. Huber, pp. 291–294. Copenhagen: Munksgaard.

Le Page, Y. & Gabe, E. J. (1979). *J. Appl. Cryst.* **12**, 464–466.

Le Page, Y., White, P. S. & Gabe, E. J. (1986). *NRCCAD. An Enhanced CAD-4 Control Program. Proc. Am. Crystallogr. Hamilton Meet.* Abstr. PA23.

Michel, A. G., Drouin, M. & Hall, D. G. (1995). *Acta Cryst.* C51, 340; addendum to *Acta Cryst.* (1993). C49, 1830–1833.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Methyl 12-Acetyl-9-methyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0²,⁷]trideca-2,4,6-triene-13-carboxylate

VIKTOR KETTMANN AND JÁN SVETLÍK

Faculty of Pharmacy, Comenius University, Odbojarov 10, Bratislava, Slovak Republic 83232. E-mail: sivy@fpharm. uniba.sk

Abstract

The title compound, $C_{15}H_{16}N_2O_4S$, represents a conformationally restricted dihydropyrimidine analogue of 1,4-dihydropyridine-type calcium antagonists and was selected for a crystal structure determination in order to clarify some aspects of structure–activity relationships. The carbonyl function of the acetyl group is oriented *cis* with respect to the C2—N3 bond, presumably to avoid repulsive interaction between the negatively charged carbonyl O and thione S atoms.

Comment

The 1,4-dihydropyridines, (1), are known to be the most potent class of calcium-channel antagonists widely used in clinical medicine. However, these compounds have a serious disadvantage in that their plasma half-lives are relatively short due to their rapid metabolic oxidation to inactive pyridines. In an effort to prolong their duration of action, new drugs based on a dihydropyrimidine-2-thione substructure, (2), have been developed (Rovnyak *et al.*, 1992). Although the pyrimidine nucleus is stable against oxidation, the vasorelaxant activity of molecules of type (2) was reported to be generally three to five times lower compared to that of type (1). For derivative (2a), this was confirmed in both *in vitro* and radioligand-binding experiments (Kettmann, Dřímal &