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# Absolute configurations of Emycin D, E and F; mimicry of centrosymmetric space groups by mixtures of chiral stereoisomers

Martina Walker,[a] Ehmke Pohl,[a,b] Regine Herbst-Irmer,[a] Martin Gerlitz,[c] Jürgen Rohr[c] and George M. Sheldrick[a]*

[a]*Institut für Anorganische Chemie der Universität Göttingen, Tammannstrasse 4, D37077 Göttingen, Germany,* [b]*EMBL Hamburg Outstation c/o DESY, Notkestrasse 85, D22603 Hamburg, Germany, and* [c]*Institut für Organische Chemie der Universität Göttingen, Tammannstrasse 2, D37077 Göttingen, Germany.*
*E-mail: gsheldr@shelx.uni-ac.gwdg.de*

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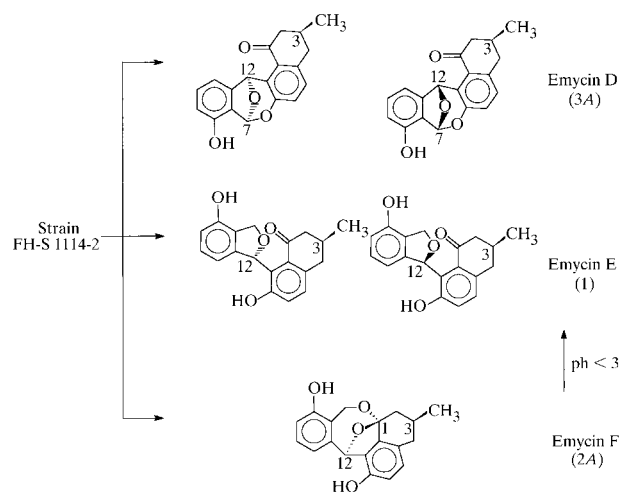
## Abstract

The crystal structures of Emycin E (1), di-*o*-bromobenzoyl-Emycin F (2) and *o*-bromobenzoyl-Emycin D (3) have been determined by X-ray analysis at low temperature. Emycin E and *o*-bromobenzoyl-Emycin D both crystallize with two molecules in a triclinic unit cell. These two structures can be solved and refined either in the centrosymmetric space group $P\bar{1}$, with apparent disorder localized at or around the expected chiral centre, or in the non-centrosymmetric space group *P*1 as mixtures of two diastereomers without disorder. Only the latter interpretation is consistent with the chemical and spectroscopic evidence. Refinements in the centrosymmetric and non-centrosymmetric space groups are compared in this paper and are shown to favour the chemically correct interpretation, more decisively so in the case of the bromo derivative as a result of the anomalous dispersion of bromine. Structures (1) and (3) provide a dramatic warning of the dangers inherent in the conventional wisdom that if a structure can be refined satisfactorarily in both centrosymmetric and non-centrosymmetric space groups, the former should always be chosen. *In these two cases, despite apparently acceptable intensity statistics and R factors (5.87 and 3.55%), the choice of the centrosymmetric space group leads to the serious chemical error that the triclinic unit cell contains a racemate rather than two chiral diastereomers!* The weakest reflections are shown to be most sensitive to the correct choice of space group, underlining the importance of refining against *all* data rather than against intensities greater than a specified threshold. The use of similar-distance restraints is shown to be beneficial in both *P*1 refinements. Di-*o*-bromobenzoyl-Emycin F crystallizes in the monoclinic space group $P2_1$ with one molecule in the asymmetric unit and so does not give rise to these problems of interpretation. The absolute configuration of the two bromo derivatives, and hence the Emycins in general, was determined unambiguously as *S* at the chiral centre C3.

## 1. Introduction

A promising approach in the search for new lead structures for antibiotics and novel chemical compounds with biological activity involves the genetic modification of organisms that are known to produce antibiotics. In the random genetic modification of selected *streptomyces*, interest is focused on polyketide producers whose product spectra are influenced by oxidoreductases. The novel compounds Emycin D (3*A*), Emycin E (1) and Emycin F (2*A*) were isolated from a mutated *streptomyces cellulosae ssp. griseoincarnatus* (FH-S 1114-2) strain (Gerlitz *et al.*, 1995*a*,*b*).




They are related to the antibiotics ochromycin and deoxyrabelomycin (Rohr & Thiericke, 1992) which are produced by the non-mutated *streptomyces cellulosae ssp. griseoincarnatus* (FH-S 1114) strain as minor products. The isolation and characterization of the Emycins by NMR techniques has been described by Gerlitz *et al.* (1995*a*,*b*). Emycin D, E and F are biosynthetic products of the strain FH-S 1114-2 and Emycin F rearranges at pH values less than 3 to the thermodynamically more stable Emycin E (Fig. 1).

The first X-ray data set for Emycin E (1) was collected routinely at room temperature without measurement of Friedel opposites. Intensity statistics suggested the centrosymmetric space group $P\bar{1}$ and the structure was successfully solved and refined in this space group, with a disordered methyl group at the expected chiral centre C3, but otherwise no suspicious features (Fig. 2). However, the NMR data of the sample used for crystallization showed a doubled set of resonances, indicating a mixture of two diastereomers instead of the racemic mixture implied by the crystal structure: optical isomers give identical NMR chemical shifts (in optically inactive solvents), but the chemical shifts of stereoisomers should be slightly different. In addition, from the proposed biosynthetic pathway and the NMR data, the compound has to consist of two non-separable diastereomers (by chiral-phase HPLC and crystallization), each of which should possess the same configuration at the chiral centre C3. Given this additional information, it is impossible for the space group to be centrosymmetric. When, however, a pseudo-inversion centre is consistent with nearly all the atomic positions, centric intensity statistics would be expected even if the true space group is $P1$. In a first attempt to resolve this problem a second data set containing all Friedel pairs was collected carefully at low temperature. As these data are clearly superior, they are used in all the subsequent work reported here.

In order to determine the absolute structure of the Emycins, two bromo derivatives were synthesized and crystallized. For both derivates complete data sets including Friedel pairs were collected at low temperature. In addition to establishing the absolute configuration of the Emycins, in the case of (3) these data also proved useful in resolving the $P1/P\bar{1}$ ambiguity.

## 2. Experimental

The isolation, synthesis and purification of (1), (2*A*), (2), (3*A*) and (3) has been described in detail by Gerlitz (1995). Crystals of (1) were obtained from ethyl acetate solution at 277 K. Crystals of (2) were grown from

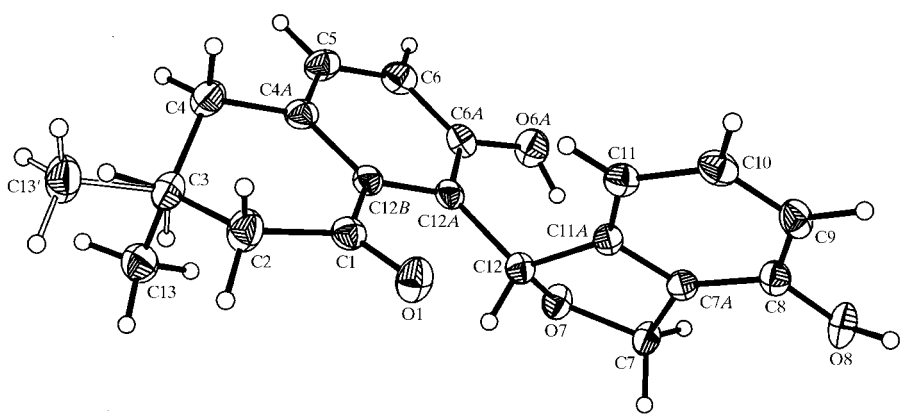



Fig. 1. Asymmetric unit of the crystal structure of Emycin E (1) refined as a disordered racemate in $P\bar{1}$.

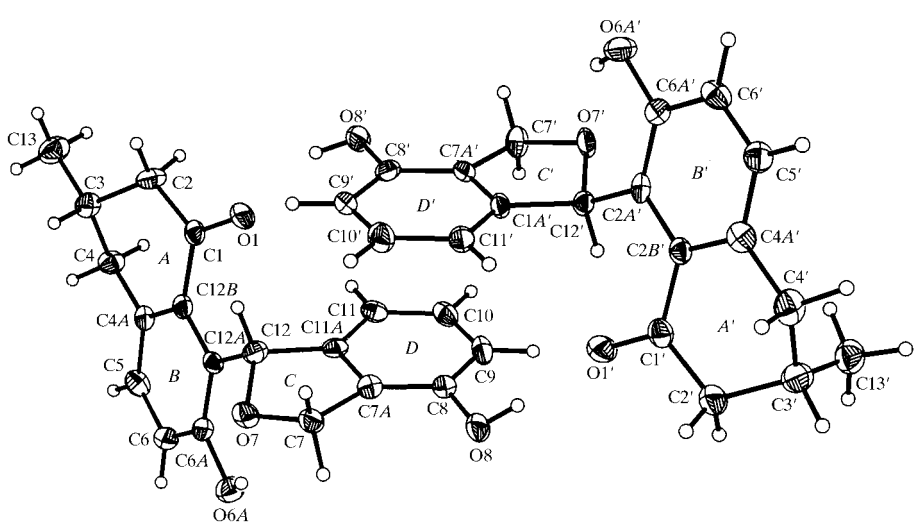



Fig. 2. Crystal structure of the two chiral diastereomers of Emycin E (1) in the $P1$ unit cell; atom-numbering scheme and 50% probablility displacement ellipsoids.

Table 1. *Experimental details*

| | (1) | (2) | (3) |
|---|---|---|---|
| Crystal data | | | |
| Chemical formula | $C_{19}H_{18}O_4$ | $C_{33}H_{24}Br_2O_6$ | $C_{26}H_{19}BrO_5$ |
| Chemical formula weight | 310.33 | 676.34 | 491.32 |
| Cell setting | Triclinic | Monoclinic | Triclinic |
| Space group | $P1$ | $P2_1$ | $P1$ |
| $a$ (Å) | 8.075 (2) | 7.796 (2) | 8.279 (2) |
| $b$ (Å) | 8.871 (2) | 7.914 (2) | 11.539 (3) |
| $c$ (Å) | 11.606 (2) | 22.243 (2) | 11.962 (3) |
| $\alpha$ (°) | 72.69 (3) | 90 | 101.32 (2) |
| $\beta$ (°) | 80.07 (3) | 92.12 (2) | 110.25 (2) |
| $\gamma$ (°) | 71.84 (3) | 90 | 92.76 (2) |
| $V$ (Å$^3$) | 751.3 (3) | 1371.4 (5) | 1042.9 (5) |
| $Z$ | 2 | 2 | 2 |
| $D_x$ (Mg m$^{-3}$) | 1.372 | 1.638 | 1.565 |
| Radiation type | Mo $K\alpha$ | Mo $K\alpha$ | Mo $K\alpha$ |
| Wavelength (Å) | 0.71073 | 0.71073 | 0.71073 |
| No. of reflections for cell parameters | 50 | 54 | 43 |
| $\theta$ range (°) | 10−12.5 | 10–12.5 | 10–12.5 |
| $\mu$ (mm$^{-1}$) | 0.096 | 3.003 | 2.009 |
| Temperature (K) | 153 (2) | 153 (2) | 153 (2) |
| Crystal form | Blocks | Blocks | Blocks |
| Crystal size (mm) | 0.4 × 0.2 × 0.2 | 0.4 × 0.2 × 0.2 | 0.4 × 0.2 × 0.2 |
| Crystal colour | Colourless | Yellow | Colourless |
| Data collection | | | |
| Diffractometer | Stoe–Siemens–Huber AED-2 four-circle | Stoe–Siemes–Huber AED-2 four-circle | Stoe–Siemens AED four-circle |
| Data collection method | Profile data from $2\theta/\omega$ scans | Profile data from $2\theta/\omega$ scans | Profile data from $2\theta/\omega$ scans |
| Absorption correction | None | Psi scan | Psi scan |
| $T_{min}$ | – | 0.203 | 0.376 |
| $T_{max}$ | – | 0.273 | 0.426 |
| No. of measured reflections | 5336 | 6184 | 6304 |
| No. of independent reflections | 5336 | 4870 | 6304 |
| No. of observed reflections | 4018 | 4144 | 5946 |
| Criterion for observed reflections | $I > 2\sigma(I)$ | $I > 2\sigma(I)$ | $I > 2\sigma(I)$ |
| $R_{int}$ | 0.0000 | 0.0385 | 0.0000 |
| $\theta_{max}$ (°) | 25.08 | 25.07 | 25.07 |
| Range of $h$, $k$, $l$ | $-9 \rightarrow h \rightarrow 9$<br>$-10 \rightarrow k \rightarrow 10$<br>$-13 \rightarrow l \rightarrow 13$ | $-9 \rightarrow h \rightarrow 9$<br>$-9 \rightarrow k \rightarrow 9$<br>$-26 \rightarrow l \rightarrow 26$ | $-9 \rightarrow h \rightarrow 9$<br>$-13 \rightarrow k \rightarrow 13$<br>$-14 \rightarrow l \rightarrow 14$ |
| No. of standard reflections | 3 | 3 | 3 |
| Frequency of standard reflections | Every 90 min | Every 90 min | Every 90 min |
| Refinement | | | |
| Refinement on | $F^2$ | $F^2$ | $F^2$ |
| $R[F^2 > 2\sigma(F^2)]$ | 0.0526 | 0.0418 | 0.0307 |
| $wR(F^2)$ | 0.1178 | 0.0966 | 0.0892 |
| $S$ | 1.033 | 1.029 | 1.298 |
| No. of reflections used in refinement | 5336 | 4870 | 6304 |
| No. of parameters used | 421 | 371 | 579 |
| H-atom treatment | Mixed | Mixed | Mixed |
| Weighting scheme | $w = 1/[\sigma^2(F_o^2) + (0.0300P)^2 + 0.8000P]$, where $P = (F_o^2 + 2F_c^2)/3$ | $w = 1/[\sigma^2(F_o^2) + (0.0439P)^2 + 1.0045P]$, where $P = (F_o^2 + 2F_c^2)/3$ | $w = 1/[\sigma^2(F_o^2) + (0.0300P)^2 + 1.3000P]$, where $P = (F_o^2 + 2F_c^2)/3$ |
| $(\Delta/\sigma)_{max}$ | 0 | 0.001 | 0 |
| $\Delta\rho_{max}$ (e Å$^{-3}$) | 0.191 | 0.374 | 0.411 |
| $\Delta\rho_{min}$ (e Å$^{-3}$) | −0.219 | −0.612 | −0.409 |
| Extinction method | None | None | None |
| Source of atomic scattering factors | *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4) | *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4) | *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4) |

Table 1 (*cont.*)

| | (1) | (2) | (3) |
|---|---|---|---|
| Computer programs | | | |
| Data collection | *DIF*4 (Stoe & Cie, 1988*a*) | *DIF*4 (Stoe & Cie, 1988*a*) | *DIF*4 (Stoe & Cie, 1988*a*) |
| Cell refinement | *DIF*4 (Stoe & Cie, 1988*a*) | *DIF*4 (Stoe & Cie, 1988*a*) | *DIF*4 (Stoe & Cie, 1988*a*) |
| Data reduction | *REDU*4 (Stoe & Cie, 1988*b*) | *REDU*4 (Stoe & Cie, 1988*b*) | *REDU*4 (Stoe & Cie, 1988*b*) |
| Structure solution | *SHELXS*90 (Sheldrick, 1990) | *SHELXS*90 (Sheldrick, 1990) | *SHELXS*90 (Sheldrick, 1990) |
| Structure refinement | *SHELXL*97 (Sheldrick, 1997) | *SHELXL*97 (Sheldrick, 1997) | *SHELXL*97 (Sheldrick, 1997) |
| Preparation of material for publication | *SHELXL*97 (Sheldrick, 1997) | *SHELXL*97 (Sheldrick, 1997) | *SHELXL*97 (Sheldrick, 1997) |

methanol/*n*-pentane (1:2) and of (3) from dichloromethane/*n*-pentane (1:2) at 298 K. The crystals were transferred into a drop of viscous perfluorinated ether (*RS*-3000 oil from Riedel de Haën) and mounted on the tip of a glass fibre using a locally built low-temperature device (Kottke & Stalke, 1993). Data were collected at 153 K for (1) and (2) on a four-circle diffractometer constructed from Huber, Stoe and Siemens components and for (3) on a Stoe-Siemens four-circle diffractometer, using graphite-monochromated Mo $K\alpha$ radiation ($\lambda$ = 0.71073 Å), equal scan widths and speeds for all reflections, and real-time profile fitting (Clegg, 1981). Accurate cell dimensions were refined against the angles of 40–60 strong reflections in the range $20 \leq 2\theta \leq 25^\circ$ centred at $+2\theta$, $+\omega$ and $-2\theta$, $-\omega$. During data collection three standard reflections were measured every 90 min; no crystal decay was observed. For (2) and (3) a semi-empirical absorption correction based on $\psi$-scans was employed. Further details of the final refinements are given in Table 1.

The structures were solved by direct methods using *SHELXS*90 (Sheldrick, 1990). All non-H atoms were refined anisotropically against all $F^2$ by full-matrix least-squares using *SHELXL*97 (Sheldrick, 1997). The H atoms were included in calculated positions and refined using a riding model. Floating origin restraints were generated automatically by the program. For reasons discussed below, the final *P*1 refinements for (1) and (3) were performed with *similar distance restraints* on chemically equivalent 1,2 and 1,3 distances. The absolute structure was determined using the method introduced by Flack (1983). All figures were drawn using the *XP* program in the *SHELXTL* system (Sheldrick, 1994).

## 3. Results and discussion

Crystal data and details of the structure refinements are presented in Table 1. Atomic coordinates and isotropic displacement parameters for the three structures are given in Tables 2–4.† Puckering parameter of non-planar rings are summarized in Table 6.

† Supplementary data for this paper are available from the IUCr electronic archives (Reference: JZ0006). Services for accessing these data are described at the back of the journal.

### 3.1. *Emycin E (1)*

Compound (1) could be refined satisfactorily both in space group *P*1 (Fig. 2) and in space group $P\bar{1}$ (Fig. 1). Although this structure can be refined without additional restraints (except for floating origin restraints in *P*1; Flack & Schwarzenbach, 1988), similar distance restraints (see below) were employed for the final *P*1 refinement. Further details are summarized in Table 5. Since the Friedel opposites were not averaged in *P*1, the data-to-parameter ratio was about the same in both space groups and the same weighting scheme was used for both. Refinement in *P*1 gave a slightly lower *R* value (0.0526 as opposed to 0.0587 in $P\bar{1}$), but the main crystallographic evidence for choosing the non-centrosymmetric space group comes from the statistics for the weak reflections. As shown in Table 5, refinement in $P\bar{1}$ resulted in unreasonably large values of $K$ = [mean($F_o^2$)/mean($F_c^2$)] for the reflections with the smallest $F_c$ values. For the smallest 1%, K was 9.487 for refinement in $P\bar{1}$ and 1.577 for refinement in *P*1. This is in keeping with the general experience that the weak reflections are most sensitive to space-group errors (Marsh, 1981) and underlines the importance of refining against all data without the imposition of a threshold. Since the chemical and spectroscopic evidence also favours the interpretation as a mixture of stereoisomers in *P*1 rather than a disordered racemic mixture in $P\bar{1}$, we conclude that the *P*1 model is the correct one. The standard uncertainties are in general lower in $P\bar{1}$; the data-to-parameter ratio is similar, but averaging of Friedel opposites reduces random errors in the data. However, the apparently disordered bond length C(3)—C(13) was unreasonably short in $P\bar{1}$.

Thermal ellipsoid plots of the two independent diastereomers in the *P*1 refinement are shown in Fig. 2. In the absence of significant dispersion terms the absolute configuration could not be determined from the Mo $K\alpha$ X-ray data, but it can be seen that the relative configuration at the chiral centre C3 is the same in both isomers and that the formation of the five-membered ring has produced two different diastereomers. The absolute configuration has been assumed to be the same as in the bromobenzoyl derivatives, with *S* at C(3), C(12), C(3′) and *R* at C(12). Atomic coordinates and equivalent isotropic displacement parameters are given

in Table 2. Bond lengths and angles in the two diastereomers are in the expected range and corresponding values in the two molecules agree within three standard deviations. The molecular structure contains four rings. Rings *B* and *D* are six-membered, planar and aromatic. The five-membered ring *C* adopts an envelope conformation (Cremer & Pople, 1975; Boessenkool & Boeyens, 1980; Gould *et al.*, 1995), with the flap at O(7) pointing down in the first diastereomer and the flap at O(7′) pointing up in the second. The six-membered ring *A* adopts a conformation intermediate between boat, twist-boat and chair. C(1), C(12*B*), C(4*A*) and C(4) in the first isomer (r.m.s. deviation 0.021 Å) and C(1′), C(2*B*′), C(4*A*′) and C(4′) in the second (r.m.s. deviation 0.012 Å) are approximately coplanar, but the atoms C(2) and C(3) in the first and C(2′) and C(3′) in the second deviate appreciably from these planes.

Compound (1) shows intra- and intermolecular interactions in the crystal packing. There are two intramolecular hydrogen bonds [H(6*A*)—O(7) 1.850, O(6*A*)—O(7) 2.580 (6) Å, O(6*A*)—H(6*A*)—O(7) 144.5°; H(6*A*′)—O(7′) 1.859, O(6*A*′)—O(7′) 2.590 (6) Å,

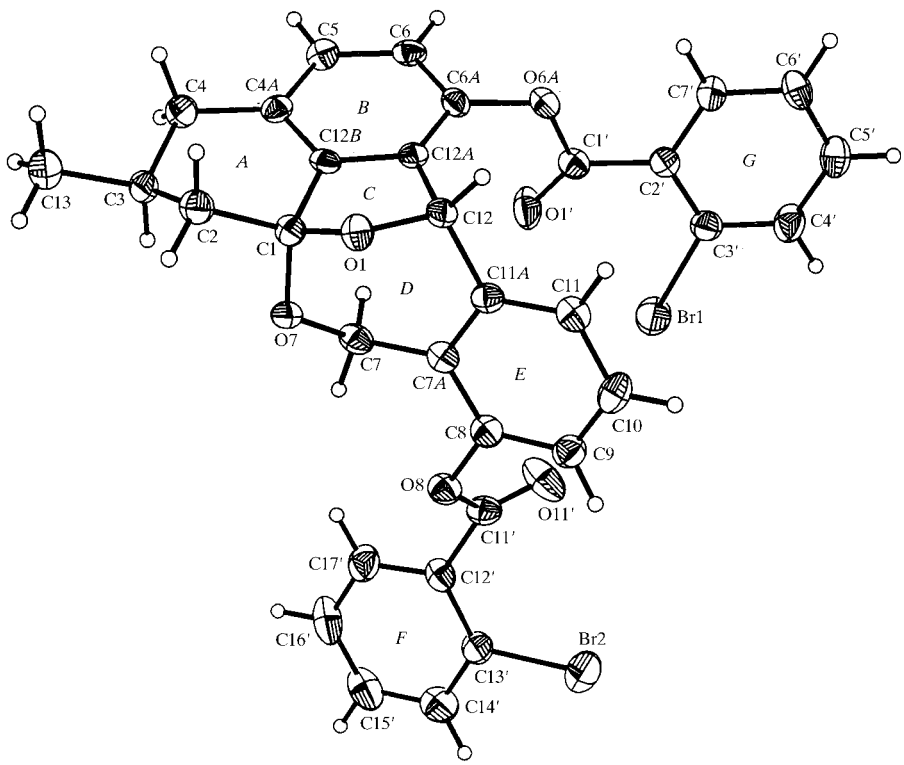



Fig. 3. Crystal structure of di-*o*-bromobenzoyl-Emycin F (2) in $P2_1$; atom numbering and 50% probability displacement ellipsoids.

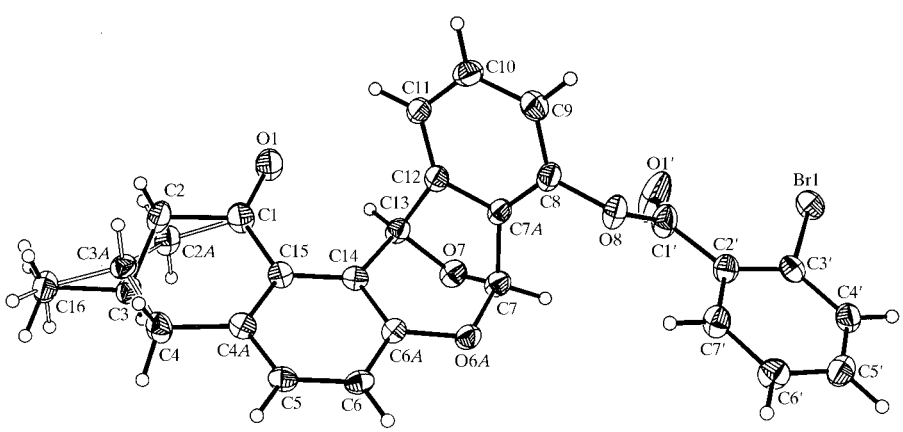



Fig. 4. Asymmetric unit of the crystal structure of *o*-bromobenzoyl-Emycin D (3) refined as a disordered racemate in $P\bar{1}$.

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for Emycin E*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$

| | *x* | *y* | *z* | $U_{eq}$ |
|---|---|---|---|---|
| O1 | 1.2807 (5) | 0.4671 (5) | 0.0429 (4) | 0.0295 (11) |
| C1 | 1.4036 (7) | 0.4809 (6) | −0.0336 (5) | 0.0201 (14) |
| C2 | 1.5307 (8) | 0.3314 (7) | −0.0646 (6) | 0.0276 (16) |
| C3 | 1.6965 (7) | 0.3589 (6) | −0.1404 (5) | 0.0241 (14) |
| C4 | 1.6411 (8) | 0.5043 (6) | −0.2485 (5) | 0.0252 (15) |
| C4*A* | 1.5353 (7) | 0.6555 (6) | −0.2088 (5) | 0.0205 (14) |
| C5 | 1.5472 (8) | 0.8096 (7) | −0.2795 (5) | 0.0249 (15) |
| C6 | 1.4557 (8) | 0.9505 (7) | −0.2437 (5) | 0.0268 (16) |
| C6*A* | 1.3507 (7) | 0.9398 (6) | −0.1355 (5) | 0.0224 (14) |
| O6*A* | 1.2669 (6) | 1.0860 (5) | −0.1085 (4) | 0.0302 (11) |
| O7 | 1.2253 (5) | 0.9084 (5) | 0.1095 (4) | 0.0230 (10) |
| C7 | 1.0646 (7) | 0.9451 (7) | 0.1866 (5) | 0.0234 (15) |
| C7*A* | 0.9356 (6) | 0.9053 (7) | 0.1304 (5) | 0.0198 (14) |
| C8 | 0.7563 (7) | 0.9394 (7) | 0.1510 (5) | 0.0224 (14) |
| O8 | 0.6749 (5) | 1.0339 (5) | 0.2297 (4) | 0.0271 (11) |
| C9 | 0.6665 (7) | 0.8842 (7) | 0.0879 (5) | 0.0233 (14) |
| C10 | 0.7589 (7) | 0.7904 (7) | 0.0081 (5) | 0.0233 (15) |
| C11 | 0.9392 (7) | 0.7496 (7) | −0.0099 (5) | 0.0207 (14) |
| C11*A* | 1.0262 (7) | 0.8097 (6) | 0.0515 (5) | 0.0194 (14) |
| C12 | 1.2195 (7) | 0.7798 (6) | 0.0567 (5) | 0.0220 (14) |
| C12*A* | 1.3320 (7) | 0.7887 (6) | −0.0617 (5) | 0.0179 (13) |
| C12*B* | 1.4251 (7) | 0.6461 (6) | −0.1007 (5) | 0.0197 (14) |
| C13 | 1.8066 (6) | 0.2064 (5) | −0.1797 (4) | 0.0375 (10) |
| O1′ | 0.4082 (5) | 0.9157 (5) | 0.3601 (4) | 0.0307 (12) |
| C1′ | 0.2874 (7) | 0.9032 (6) | 0.4390 (5) | 0.0227 (15) |
| C2′ | 0.1687 (8) | 1.0571 (7) | 0.4683 (6) | 0.0289 (15) |
| C3′ | 0.0010 (8) | 1.0407 (7) | 0.5484 (5) | 0.0290 (15) |
| C4′ | 0.0481 (8) | 0.8894 (6) | 0.6540 (5) | 0.0294 (16) |
| C4*A*′ | 0.1476 (7) | 0.7354 (6) | 0.6153 (5) | 0.0232 (14) |
| C5′ | 0.1312 (8) | 0.5834 (6) | 0.6852 (5) | 0.0254 (15) |
| C6′ | 0.2213 (7) | 0.4417 (7) | 0.6538 (5) | 0.0241 (15) |
| C6*A*′ | 0.3311 (7) | 0.4465 (6) | 0.5467 (5) | 0.0230 (15) |
| O6*A*′ | 0.4175 (6) | 0.2993 (5) | 0.5210 (4) | 0.0312 (11) |
| O7′ | 0.4586 (5) | 0.4714 (5) | 0.3001 (4) | 0.0248 (11) |
| C7′ | 0.6191 (7) | 0.4354 (8) | 0.2212 (5) | 0.0235 (15) |
| C7*A*′ | 0.7461 (6) | 0.4774 (7) | 0.2773 (5) | 0.0194 (14) |
| C8′ | 0.9270 (7) | 0.4403 (7) | 0.2552 (5) | 0.0210 (14) |
| O8′ | 1.0052 (5) | 0.3514 (5) | 0.1721 (4) | 0.0297 (11) |
| C9′ | 1.0184 (8) | 0.4946 (7) | 0.3180 (6) | 0.0271 (16) |
| C10′ | 0.9298 (7) | 0.5836 (8) | 0.4010 (6) | 0.0268 (15) |
| C11′ | 0.7483 (7) | 0.6224 (7) | 0.4203 (5) | 0.0230 (14) |
| C1*A*′ | 0.6598 (6) | 0.5693 (7) | 0.3566 (5) | 0.0182 (14) |
| C12′ | 0.4650 (6) | 0.6015 (6) | 0.3522 (5) | 0.0184 (13) |
| C2*A*′ | 0.3508 (7) | 0.5956 (6) | 0.4709 (5) | 0.0211 (14) |
| C2*B*′ | 0.2613 (7) | 0.7408 (6) | 0.5084 (5) | 0.0193 (13) |
| C13′ | −0.1375 (5) | 1.0327 (5) | 0.4774 (4) | 0.0336 (10) |

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²) for di-o-bromobenzyl-Emycin F*

$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$

| | *x* | *y* | *z* | $U_{eq}$ |
|---|---|---|---|---|
| Br1 | 0.53656 (7) | −0.26337 (10) | 0.62293 (3) | 0.0618 (2) |
| Br2 | 0.84803 (7) | 0.38811 (8) | 0.53382 (3) | 0.05315 (18) |
| O1 | 0.8591 (4) | −0.0143 (4) | 0.91404 (13) | 0.0246 (7) |
| O7 | 1.0971 (4) | −0.0192 (4) | 0.85444 (13) | 0.0254 (7) |
| O6*A* | 0.5546 (4) | −0.4198 (4) | 0.82114 (13) | 0.0242 (7) |
| O1′ | 0.6948 (4) | −0.3811 (6) | 0.73638 (15) | 0.0431 (10) |
| O8 | 0.9624 (4) | 0.1616 (4) | 0.69371 (14) | 0.0286 (7) |
| O11′ | 0.8264 (5) | 0.0459 (5) | 0.61244 (16) | 0.0475 (11) |
| C1 | 1.0182 (5) | −0.0994 (7) | 0.90366 (19) | 0.0223 (9) |
| C2 | 1.1465 (5) | −0.0968 (7) | 0.95567 (19) | 0.0278 (10) |
| C3 | 1.2901 (5) | −0.2260 (6) | 0.94372 (19) | 0.0266 (11) |
| C13 | 1.4310 (6) | −0.2182 (7) | 0.9931 (2) | 0.0363 (12) |
| C4 | 1.2220 (6) | −0.4080 (6) | 0.9361 (2) | 0.0262 (10) |
| C4*A* | 1.0527 (6) | −0.4224 (6) | 0.90237 (19) | 0.0232 (10) |
| C5 | 0.9705 (6) | −0.5720 (6) | 0.88573 (19) | 0.0255 (11) |
| C6 | 0.8072 (6) | −0.5714 (6) | 0.85882 (19) | 0.0248 (10) |
| C6*A* | 0.7185 (5) | −0.4229 (6) | 0.84966 (19) | 0.0231 (10) |
| C7 | 1.0241 (5) | −0.0468 (6) | 0.79540 (19) | 0.0264 (10) |
| C7*A* | 0.8499 (5) | 0.0307 (6) | 0.78141 (19) | 0.0218 (10) |
| C8 | 0.8213 (6) | 0.1269 (6) | 0.7295 (2) | 0.0265 (10) |
| C9 | 0.6627 (6) | 0.1978 (6) | 0.7138 (2) | 0.0295 (11) |
| C10 | 0.5240 (6) | 0.1655 (7) | 0.7490 (2) | 0.0315 (12) |
| C11 | 0.5475 (6) | 0.0670 (6) | 0.8004 (2) | 0.0270 (11) |
| C11*A* | 0.7071 (6) | 0.0031 (6) | 0.8165 (2) | 0.0229 (10) |
| C12 | 0.7286 (5) | −0.0928 (6) | 0.87512 (18) | 0.0230 (10) |
| C12*A* | 0.7930 (5) | −0.2728 (6) | 0.86923 (17) | 0.0198 (9) |
| C12*B* | 0.9590 (5) | −0.2764 (6) | 0.89062 (17) | 0.0203 (9) |
| C1′ | 0.5601 (6) | −0.3978 (6) | 0.7598 (2) | 0.0258 (11) |
| C2′ | 0.3883 (5) | −0.3991 (6) | 0.7300 (2) | 0.0228 (10) |
| C3′ | 0.3591 (6) | −0.3446 (6) | 0.6709 (2) | 0.0285 (11) |
| C4′ | 0.1966 (6) | −0.3449 (7) | 0.6446 (2) | 0.0358 (13) |
| C5′ | 0.0612 (6) | −0.4023 (7) | 0.6763 (2) | 0.0338 (12) |
| C6′ | 0.0860 (6) | −0.4615 (6) | 0.7343 (2) | 0.0306 (11) |
| C7′ | 0.2488 (6) | −0.4580 (6) | 0.7605 (2) | 0.0266 (11) |
| C11′ | 0.9444 (6) | 0.1224 (6) | 0.6340 (2) | 0.0293 (11) |
| C12′ | 1.0921 (6) | 0.1860 (6) | 0.6006 (2) | 0.0273 (11) |
| C13′ | 1.0679 (6) | 0.3003 (7) | 0.5533 (2) | 0.0318 (12) |
| C14′ | 1.2035 (7) | 0.3562 (8) | 0.5205 (2) | 0.0421 (15) |
| C15′ | 1.3655 (7) | 0.2954 (8) | 0.5346 (2) | 0.0443 (15) |
| C16′ | 1.3937 (6) | 0.1837 (8) | 0.5805 (2) | 0.0459 (16) |
| C17′ | 1.2571 (6) | 0.1302 (8) | 0.6141 (2) | 0.0373 (12) |

O(6*A*′)—H(6*A*′)—O(7′) 144.5°] and two intermolecular hydrogen bonds [H(8)—O(1′) 1.877, O(8)—O(1′) 2.714 (6) Å, O(8)—H(8)—O(1′) 174.0°; H(8′)—O(1) 1.967, O(8′)—O(1) 2.758 (6) Å, O(8′)—H(8′)—O(1) 156.7°].

### 3.2. *Di-o-bromobenzoyl-Emycin F (2)*

Compound (2) crystallizes in space group $P2_1$ with one molecule in the asymmetric unit. Refinement in the centrosymmetric space group $P2_1/m$ is not possible as the molecule does not possess any symmetry. In this case only one diastereomer was produced in the biosynthesis. Atomic coordinates and equivalent isotropic displacement parameters are given in Table 3. Fig. 3 shows the molecular structure which contains seven rings, of which *F*, *G*, *B* and *E* are six-membered, planar and aromatic. Ring *D* is seven-membered with C(7), C(7*A*), C(11*A*), C(12) coplanar (r.m.s. deviation 0.022 Å). In the six-membered ring *A* the atoms C(1), C(12*B*), C(4*A*) and C(4) are coplanar (r.m.s. deviation 0.019 Å). The absolute structure was determined by refinement of the Flack (1983) *x* parameter to a value of −0.017 (10), corresponding to an *S* configuration at the chiral centre C(3) and *R* at C(1) and C(12).

Table 4. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å$^2$) for o-bromobenzoyl-Emycin D*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U^{ij} a^i a^j \mathbf{a}_i.\mathbf{a}_j.$$

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| Br1 | 1.08650 (6) | 1.05612 (4) | 1.14244 (4) | 0.0317 (2) |
| O1 | 1.2784 (7) | 0.5963 (5) | 0.3668 (5) | 0.0329 (14) |
| C1 | 1.1493 (9) | 0.5246 (6) | 0.3032 (6) | 0.0240 (16) |
| C2 | 1.1498 (7) | 0.4276 (5) | 0.1996 (5) | 0.0282 (13) |
| C3 | 0.9955 (7) | 0.4248 (5) | 0.0826 (4) | 0.0251 (11) |
| C16 | 0.9931 (12) | 0.3249 (7) | −0.0228 (7) | 0.0314 (19) |
| C4 | 0.8257 (9) | 0.4121 (6) | 0.1044 (6) | 0.0261 (17) |
| C4*A* | 0.8290 (9) | 0.4829 (7) | 0.2264 (6) | 0.0231 (18) |
| C5 | 0.6716 (9) | 0.4943 (7) | 0.2440 (6) | 0.0254 (18) |
| C6 | 0.6708 (10) | 0.5485 (6) | 0.3579 (6) | 0.0264 (19) |
| C6*A* | 0.8235 (9) | 0.5935 (6) | 0.4539 (5) | 0.0201 (16) |
| O6*A* | 0.8105 (7) | 0.6445 (5) | 0.5645 (4) | 0.0247 (12) |
| C7 | 0.9762 (9) | 0.6934 (6) | 0.6610 (6) | 0.0247 (17) |
| O7 | 1.0988 (7) | 0.6159 (4) | 0.6545 (4) | 0.0258 (13) |
| C7*A* | 1.0475 (10) | 0.8052 (5) | 0.6376 (6) | 0.0234 (17) |
| C8 | 1.0233 (10) | 0.9238 (5) | 0.6652 (7) | 0.0254 (18) |
| O8 | 0.9113 (7) | 0.9580 (5) | 0.7270 (5) | 0.0280 (13) |
| C9 | 1.1014 (11) | 1.0080 (6) | 0.6261 (7) | 0.0288 (19) |
| C10 | 1.2038 (11) | 0.9717 (6) | 0.5580 (7) | 0.0277 (19) |
| C11 | 1.2302 (11) | 0.8538 (6) | 0.5299 (7) | 0.0287 (19) |
| C12 | 1.1507 (10) | 0.7720 (5) | 0.5713 (6) | 0.0242 (18) |
| C13 | 1.1407 (10) | 0.6378 (6) | 0.5511 (6) | 0.0269 (19) |
| C14 | 0.9823 (9) | 0.5859 (6) | 0.4391 (5) | 0.0212 (17) |
| C15 | 0.9843 (8) | 0.5306 (6) | 0.3232 (5) | 0.0202 (16) |
| C1′ | 0.9692 (9) | 0.9577 (8) | 0.8488 (6) | 0.033 (2) |
| O1′ | 1.1139 (8) | 0.9454 (9) | 0.9035 (6) | 0.086 (3) |
| C2′ | 0.8275 (9) | 0.9766 (6) | 0.8961 (6) | 0.0272 (19) |
| C3′ | 0.8583 (8) | 1.0134 (6) | 1.0215 (5) | 0.0237 (18) |
| C4′ | 0.7245 (9) | 1.0224 (6) | 1.0646 (6) | 0.0260 (19) |
| C5′ | 0.5563 (11) | 0.9946 (7) | 0.9834 (7) | 0.033 (2) |
| C6′ | 0.5205 (10) | 0.9585 (7) | 0.8592 (6) | 0.0278 (18) |
| C7′ | 0.6549 (10) | 0.9503 (7) | 0.8169 (7) | 0.033 (2) |
| Br2 | 1.51559 (5) | 0.21961 (4) | 0.27707 (4) | 0.03030 (19) |
| O101 | 1.3171 (8) | 0.6661 (5) | 1.0570 (5) | 0.0364 (15) |
| C101 | 1.4451 (9) | 0.7321 (6) | 1.1265 (6) | 0.0234 (16) |
| C102 | 1.4442 (7) | 0.8068 (5) | 1.2456 (5) | 0.0278 (13) |
| C103 | 1.5955 (7) | 0.9032 (5) | 1.3113 (4) | 0.0265 (12) |
| C116 | 1.5946 (12) | 0.9642 (7) | 1.4375 (7) | 0.035 (2) |
| C104 | 1.7621 (9) | 0.8508 (6) | 1.3217 (6) | 0.0251 (17) |
| C14*A* | 1.7649 (8) | 0.7896 (6) | 1.1995 (6) | 0.0203 (17) |
| C105 | 1.9175 (9) | 0.7805 (6) | 1.1787 (6) | 0.0217 (17) |
| C106 | 1.9249 (9) | 0.7296 (6) | 1.0665 (6) | 0.0211 (17) |
| C16*A* | 1.7680 (9) | 0.6855 (6) | 0.9701 (5) | 0.0218 (17) |
| O16*A* | 1.7810 (7) | 0.6349 (4) | 0.8580 (4) | 0.0275 (13) |
| C107 | 1.6162 (9) | 0.5877 (6) | 0.7616 (6) | 0.0286 (19) |
| O107 | 1.4950 (7) | 0.6647 (5) | 0.7704 (5) | 0.0282 (13) |
| C17*A* | 1.5445 (10) | 0.4742 (5) | 0.7813 (6) | 0.0233 (17) |
| C108 | 1.5701 (10) | 0.3572 (6) | 0.7519 (7) | 0.0264 (18) |
| O108 | 1.6827 (8) | 0.3238 (5) | 0.6899 (5) | 0.0316 (14) |
| C109 | 1.4904 (11) | 0.2714 (6) | 0.7883 (7) | 0.0304 (19) |
| C110 | 1.3881 (11) | 0.3047 (6) | 0.8568 (7) | 0.033 (2) |
| C111 | 1.3629 (10) | 0.4229 (6) | 0.8893 (6) | 0.0245 (17) |
| C112 | 1.4391 (9) | 0.5069 (6) | 0.8484 (6) | 0.0234 (17) |
| C113 | 1.4505 (9) | 0.6398 (5) | 0.8716 (5) | 0.0205 (16) |
| C114 | 1.6100 (8) | 0.6906 (6) | 0.9855 (5) | 0.0210 (17) |
| C115 | 1.6096 (8) | 0.7387 (6) | 1.1025 (5) | 0.0197 (16) |
| C11′ | 1.6287 (9) | 0.3264 (8) | 0.5693 (6) | 0.032 (2) |
| O11′ | 1.4891 (8) | 0.3521 (6) | 0.5165 (6) | 0.0445 (15) |
| C12′ | 1.7702 (8) | 0.3051 (6) | 0.5219 (5) | 0.0222 (17) |
| C13′ | 1.7410 (9) | 0.2635 (6) | 0.3976 (5) | 0.0244 (19) |
| C14′ | 1.8795 (10) | 0.2505 (7) | 0.3597 (7) | 0.030 (2) |
| C15′ | 2.0476 (9) | 0.2776 (6) | 0.4417 (6) | 0.0260 (18) |
| C16′ | 2.0798 (10) | 0.3211 (7) | 0.5643 (7) | 0.0305 (19) |
| C17′ | 1.9412 (8) | 0.3340 (7) | 0.6036 (6) | 0.0238 (17) |

### 3.3. *o-Bromobenzoyl-Emycin D (3)*

As observed for (1), it is possible to refine (3) either in $P\bar{1}$ or $P1$. In the centrosymmetric case the structure is described by one molecule in the asymmetric unit and exhibits apparent disorder of the atoms C(2) and C(3) (Fig. 5). The alternative refinement of (3) in the non-centrosymmetric space group $P1$ shows two diastereomers without any disorder and with the same absolute configuration at the chiral C3 [labelled C(3) in the first and C(103) in the second molecule] (Fig. 5). It was necessary to apply similar distance restraints to the disordered region in order to obtain convergence in the $P\bar{1}$ refinement. Although no restraints were required for convergence of the non-disordered structure in $P1$ (except the floating origin restraints generated automatically by the program), similar distance restraints were employed in the final refinement. In contrast to the refinement of (1), the significant anomalous dispersion of bromine enabled the absolute configuration to be established by refinement of the Flack $x$ parameter [to −0.009 (11)], which is also a strong indication that the non-centrosymmetric space group is correct. Further evidence for $P1$ as opposed to $P\bar{1}$ is provided by the lower $R$ factor (0.0307 against 0.0355) and the statistics for the weak reflections (Table 5). The absolute configuration at the chiral centre C3 is determined to be *S* in agreement with the result for (2) and *S* at C(7), C(12) in one diastereomer and *R* at C(107), C(112) in the other. Atomic coordinates and isotropic displacement parameters are given in Table 4.

In the *ORTEP*-style plots (Johnson, 1965) of the $P1$ refinement of (3), O(1′) and to a lesser extent the pseudo-symmetry-related O(11′) show ellipsoids extended perpendicular to the carbonyl planes. Although the $U^{ij}$ parameters of these atoms will be correlated with each other, the extension of the ellipsoids is consistent with a chemically acceptable motion of the atoms. The largest correlation coefficients in the $P1$ refinement are 0.86 and link the corresponding $U^{ij}$ components of pseudo-symmetry related atoms.

Each molecule consists of six rings; the six-membered rings *B*, *E* and *F* are planar and aromatic. The five-membered ring *D* adopts an envelope conformation with the flap at O(7) pointing up in the first isomer and the flap at O(107) pointing down in the second. The six-membered ring *C* adopts a conformation intermediate between boat and chair, and the six-membered ring *A* between boat, twist-boat and chair. Equivalent bond

Table 5. *Comparison of the refinement of Emycin E (1) and o-bromobenzoyl-Emycin D (3) in P$\bar{1}$ and P1*

| | (1) | (1) | (3) | (3) |
|---|---|---|---|---|
| Space group | $P\bar{1}$ | $P1$ | $P\bar{1}$ | $P1$ |
| Reflections collected | 5336 | 5336 | 6304 | 6304 |
| Independent reflections | 2669 | 5336 | 3687 | 6304 |
| No. of parameters | 221 | 421 | 307 | 579 |
| No. of restraints | 0 | 68 | 8 | 96 |
| $R_{int}$ | 0.0413 | – | 0.0286 | – |
| $S$ | 1.318 | 1.033 | 1.136 | 1.298 |
| $R1$ [$I > 2\sigma(I)$] | 0.0587 | 0.0526 | 0.0355 | 0.0307 |
| $wR2$ [for all data] | 0.1520 | 0.1178 | 0.0854 | 0.0892 |
| Max./min. (e Å$^{-3}$) | 0.19/−0.22 | 0.19/−0.22 | 0.77/−0.41 | 0.41/−0.41 |
| $g1$ | 0.0300 | 0.0300 | 0.0300 | 0.0300 |
| $g2$ | 0.8000 | 0.8000 | 1.300 | 1.300 |
| $K[F_c/F_c(\max)\ 0.00 - 0.01]$† | **9.487** | 1.577 | 2.304 | 1.074 |
| $K[F_c/F_c(\max)\ 0.01 - 0.02]$† | 2.390 | 1.012 | 1.241 | 0.968 |
| $K[F_c/F_c(\max)\ 0.18 - 1.00]$† | 0.978 | 0.994 | 0.996 | 1.002 |
| Flack $x$ parameter | | | – | −0.009 (11) |

† $K$ = Mean $(F_o^2)$/Mean$(F_c^2)$.

lengths and angles of the two diasteromers are equal within three e.s.d.'s. All values are in the expected range and are consistent with those found in the structures of (1) and (2).

### 3.4. *Similar distance restraints*

Since the two stereoisomers in (1) are chemically very similar, it is reasonable to assume that chemically equivalent distances in the two molecules are identical within a specified standard uncertainty: the same applies to the two stereoisomers in (3). The refinement program *SHELXL* (Sheldrick, 1997) allows such restraints to be generated automatically for 1,2 and 1,3 distances by specifying a single 'SAME' instruction. Including extra chemical knowledge in the refinement in this way should improve the precision of the resulting molecular geometry and should suppress refinement instabilities arising from the presence of nearly zero eigenvalues of the least-squares normal matrix in such pseudo-centrosymmetric structures.

Table 7 shows the results of refining (1) and (3) with and without these similar distance restraints using the default *SHELXL* (Sheldrick, 1997) standard uncertainties of 0.02 Å for 1,2 and 0.04 Å for 1,3 distances. The addition of these restraints had a neglible effect on $R$ values and improved the convergence of the refinements; it also reduced the deviations between equivalent

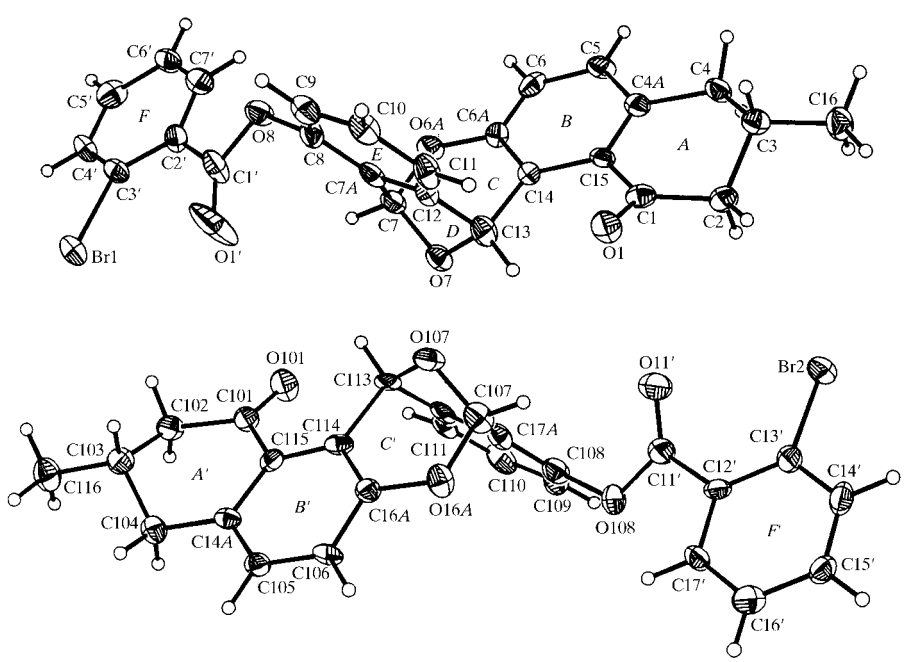



Fig. 5. Crystal structure of the two chiral diastereomers of *o*-bromobenzoyl-Emycin D (3) in the $P1$ unit cell; atom-numbering scheme and 50% probability displacement ellipsoids.

Table 6. *Cremer & Pople (1975) puckering parameter of non-planar rings*

| | (1) | (1) | (2) | (3) | (3) |
|---|---|---|---|---|---|
| Ring *A* | $q2 = 0.483$<br>$\varphi2 = 227.1$<br>$q3 = 0.232$ | $q2 = 0.429$<br>$\varphi2 = 46.1$<br>$q3 = -0.220$ | $q2 = 0.353$<br>$\varphi2 = 48.1$<br>$q3 = -0.329$ | $q2 = 0.309$<br>$\varphi2 = 279.3$<br>$q3 = 0.317$ | $q2 = 0.454$<br>$\varphi2 = 310.2$<br>$q3 = -0.216$ |
| Ring *C* | $q2 = 0.277$<br>$\varphi2 = 183.3$ | $q2 = 0.286$<br>$\varphi2 = 5.5$ | $q2 = 0.310$<br>$\varphi2 = 11.7$ | $q2 = 1.047$<br>$\varphi2 = 285.0$<br>$q3 = 0.360$ | $q2 = 0.495$<br>$\varphi2 = 1.9$<br>$q3 = 0.357$ |
| Ring *D* | | | $q2 = 0.292$<br>$\varphi2 = 116.3$<br>$q3 = 0.688$ | $q2 = 0.399$<br>$\varphi2 = 358.4$ | $q2 = 0.391$<br>$\varphi2 = 178.4$ |

Table 7. *Comparison of refinements with and without similar distance restraints in space group P1*

| Structure | (1) | (1) | (3) | (3) |
|---|---|---|---|---|
| No. of similarity restraints | 0 | 65 | 0 | 93 |
| $R1(F > 4\sigma F)$ | 0.0526 | 0.0526 | 0.0306 | 0.0307 |
| $R1$ | 0.0779 | 0.0779 | 0.0334 | 0.0334 |
| r.m.s. ($\Delta$) Å | 0.0131 | 0.0081 | 0.0255 | 0.0106 |
| r.m.s. (s.u.) Å | 0.0113 | 0.0090 | 0.0152 | 0.0107 |
| r.m.s. ($\Delta$/s.u.) | 1.149 | 0.901 | 1.743 | 1.008 |

$\Delta$ is the difference between equivalent bond lengths, s.u. the standard uncertainty of this difference; r.m.s. the root mean square.

distances and improved the agreement between the bond lengths and their values in related structures. For structure (1) the root mean square (r.m.s.) value of ($\Delta$/s.u.) (where $\Delta$ is the difference between equivalent bond lengths and s.u. is the standard uncertainty of this difference derived by the least-squares analysis) of 1.149 would still be acceptable for the unrestrained refinement, but for (3) it is too large (1.743) for the unrestrained but (fortuitously) optimal (1.008) for the restrained refinement. Structure (3) also shows a larger improvement in the precision of the structure determination when these restraints are included. The presence of the Br atoms in (3) makes this structure more pseudo-centrosymmetric than (1) because the deviations from centrosymmetry constitute a smaller fraction of the total scattering power. We conclude that the application of similar distance restraints is justified and desirable in both structure determinations, and indeed obligatory in (3) to avoid significant geometrical distortions. The unrestrained refinement of (3) leads to a warning from the *Acta Crystallographica* CHECKCIF suite that one of the bond lengths was outside the expected range: however, both restrained and unrestrained refinements of both structures in $P1$ lead of course to warnings from CHECKCIF that an inversion centre may have been overlooked!

## 4. Conclusions

The choice of $P\bar{1}$ or $P1$ as space group is not dictated by systematic absences and X-ray data are notoriously insensitive to small deviations from centrosymmetry. If a satisfactory refinement is possible in the centrosymmetric space group, the prevailing wisdom (Marsh, 1986) is that this space group should be chosen, even if it involves disorder of a minor part of the structure. We suggest that the structure determinations presented here, combined with the chemical evidence, provide a convincing demonstration of the dangers inherent in this approach. In the case of compounds (1) and (3), assumption of the centrosymmetric space group leads to apparently normal refinements ($R = 0.0587$ and 0.0355, respectively) with only very minor disorder of one or two atoms, *but the resulting structures are chemically seriously in error!*

The mean $\langle|E^2 - 1|\rangle$ value of 0.978 for (1) also indicates, *incorrectly*, a centrosymmetric space group (the expected value is 0.968 for centrosymmetric and 0.736 for non-centrosymmetric); the value of 0.740 for (2) is close to the expected non-centrosymmetric value and the value of 0.829 for (3) is intermediate. Clearly in (1) and (3) the pseudo-centrosymmetric relation between the two diastereomers leads to misleading intensity statistics; (2) behaves normally because only one diastereomer is present in the crystal. A better guide than these statistics and the final $R$ factors are the statistics for the weakest reflections, which clearly indicate that something is seriously amiss with the $P\bar{1}$ refinement of (1). *It should be noted that refinement against intensities or F values greater than a specified threshold would have thrown away the most decisive experimental information!* In addition, the successful determination of the absolute configuration of (3) by

refinement of the Flack $x$ parameter supports the assignment of the space group $P1$ rather than $P\bar{1}$.

Despite the disastrous consequences of choosing the centrosymmetric space group in these examples, we should emphasize that in other cases this could well have been the correct choice; every borderline case should be considered carefully in the light of *all* the available evidence. Even the application of similar distance restraints for the refinement in the non-centrosymmetric space group is not without risk: there is a danger that it could suppress typical warning signs of an overlooked real centre of symmetry, such as unstable refinement and geometrical distortions!

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