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Synthesis of the DE-ring of goniodomin A and prediction of its natural relative stereochemistry

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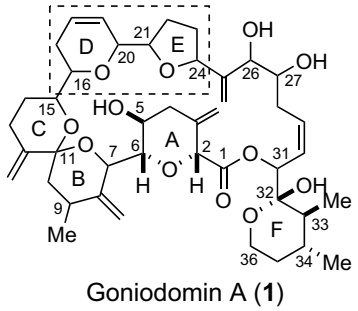
Abstract

Goniodomin A (**1**) was first isolated from *Alexandrium hiranoi* as a stereochemically unidentified antifungal agent in 1987 by Murakami. In this study, two stereoisomeric series of non-macrocyclic and macrocyclic DE-ring model compounds of **1** were synthesized, and the natural relative stereochemistry of the DE-ring was predicted by NMR comparison of **1** with these model compounds.

Keywords: Goniodomin A; Polyether macrolide; Ireland–Claisen rearrangement; NMR analysis; Natural product synthesis

Goniodomin A (**1**, Fig. 1), isolated first from dinoflagellate *Alexandrium hiranoi* as an antifungal agent by Murakami[1] and later from *A. monilatium* by Moeller and coworkers,[2] possesses remarkable bioactivity toward actin organization.[3–5] Although the unique planar structure of **1**, featuring a 32-membered macrolactone including 5- and 6-membered cyclic ethers, a spirocyclic acetal, and a 6-membered cyclic hemiacetal, was determined by Murakami, its stereochemistry has not yet been clarified. Lack of stereochemical information for **1** arrests further biological studies to elucidate the mechanism of its action. Therefore, we have launched a program for the determination of the full absolute configuration of **1** by total synthesis. Previously, we confirmed the natural relative stereochemistry of the A- and F-rings of **1** by NMR comparison of **1** and synthetic A- and F-ring model compounds having unambiguous stereochemistry.[6] We next focus our attention on the stereochemistry of the DE-ring of **1**. We describe herein the synthesis of DE-ring model compounds with and without a macrocyclic ring and the prediction of the natural relative stereochemistry of the DE-ring by NMR comparison of **1** and these model compounds.



Goniodomin A (**1**)

Fig. 1.

First, we deduced the cis-configuration of the D-ring and the trans-configuration of the E-ring from Murakami's NMR data of **1** showing the presence of an NOE interaction between H16 and H20 and the absence of an NOE between H21 and H24.[1a,b] Therefore, two possible configurations, **1a** and **1b** (Fig. 2), for the stereochemical relationship between the D- and E-rings were derived. We next planned to synthesize DE-ring models **2a** and **2b** (Fig. 3), corresponding to **1a** and **1b**, respectively, to elucidate the correct stereochemistry of the D- and E-rings by

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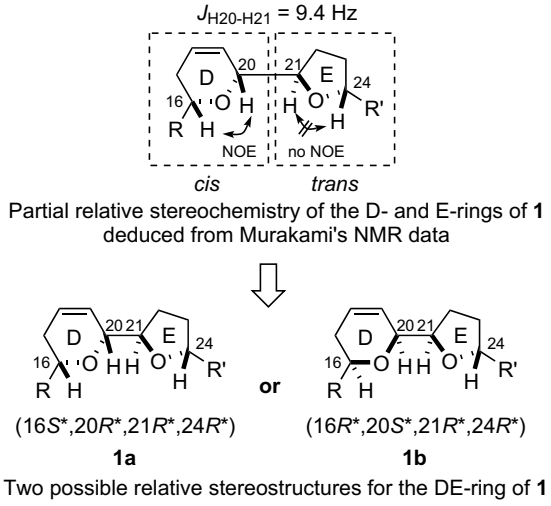


Fig. 2.

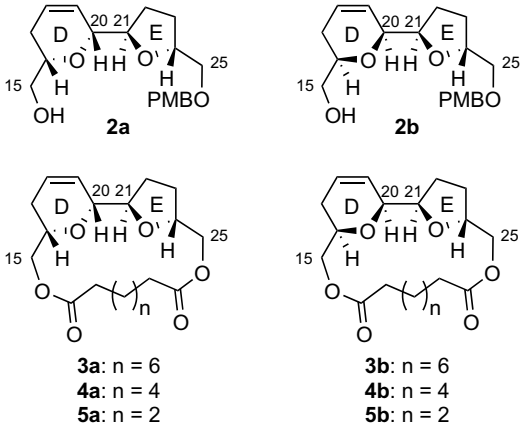
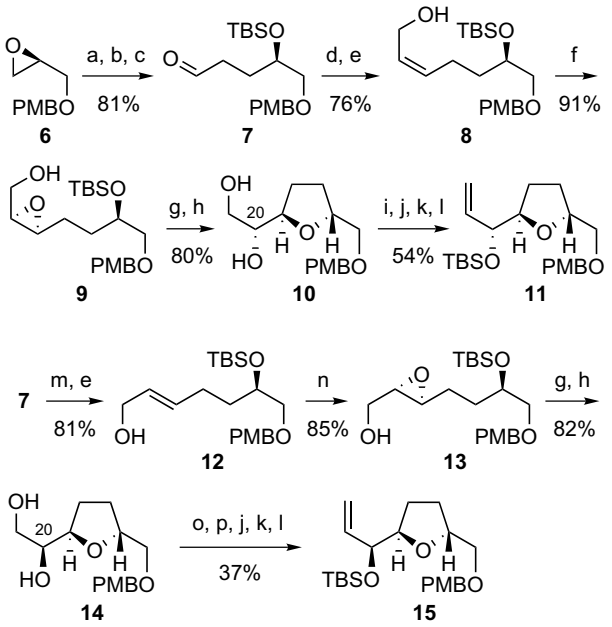


Fig. 3.

comparison of the $J_{H20–H21}$ values of **1** and the models. Unfortunately, both the models synthesized had considerably different values of $J_{H20–H21}$ (**2a**: 5.9 Hz, **2b**: 6.6 Hz) from that of **1** (9.4 Hz),[1a,b] and the relative stereochemistry of the DE-ring could not be established (as described below). Since this failure is likely caused by the lack of a macrocyclic ring in the models, we transformed **2a** and **2b** to the corresponding macrocyclic compounds **3**–**5a** and **3**–**5b** (Fig. 3) for a more precise evaluation of the relative stereochemistry at C20 and C21 of **1**.

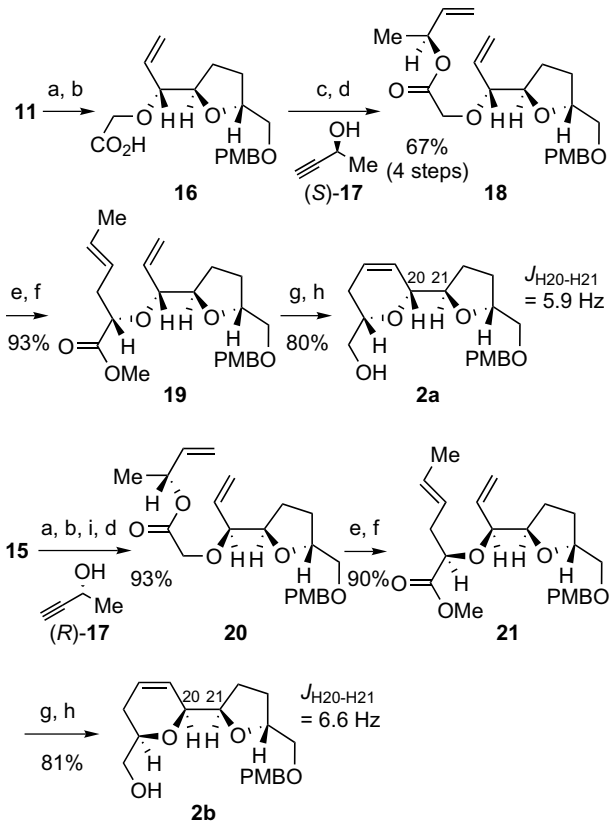
In the synthesis of **2a** and **2b**, we first undertook the construction of the E-ring by intramolecular 5-*exo* opening of a 24-hydroxy-20,21-epoxide to establish the configurations at C20 and C21 (Scheme 1). Therefore, intermediate E-ring **11** for **2a** was synthesized from cis-epoxide **9**, prepared from **6**. Epoxide **6** was initially converted to **7** (81%) by allylation, TBS-protection, and oxidative cleavage of the alkene part. Modified Horner–Wadsworth–Emmons reaction[7] of **7** followed by DIBAH reduction selectively produced *Z*-allyl alcohol **8** (76%), which was then epoxidized by the Katsuki–Sharpless procedure[8] using (−)-DET to



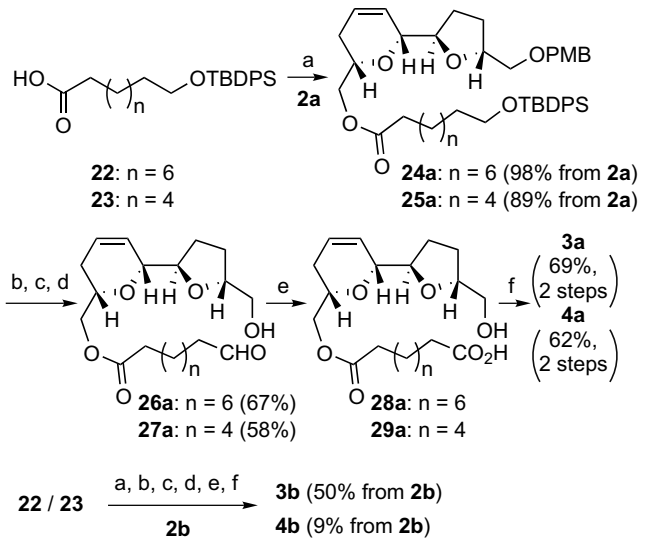
Scheme 1. Reagents and conditions: (a) allylmagnesium bromide, CuCN, THF, −20 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C; (c) OsO_4, NMO, THF–H_2O (2:1), 23 °C, then $NaIO_4$; (d) $(PhO)_2P(O)CH_2CO_2Et$, NaH, THF, −78 °C, then **7**, −78→−20 °C; (e) DIBAH, Et_2O, −78 °C; (f) TBHP, (−)-DET, Ti(O*i*-Pr)$_4$, MS4A, CH_2Cl_2, −25 °C; (g) TBAF, THF; (h) CSA, CH_2Cl_2, 0 °C; (i) PivCl, pyridine, CH_2Cl_2, 0 °C, then TBSOTf, 0 °C; (j) DIBAH, CH_2Cl_2, −78 °C; (k) DMPI, CH_2Cl_2, 23 °C; (l) Ph_3PCH_3Br, NHMDS, 23 °C, then aldehyde, −78→23°C; (m) Ph_3PCHCO_2Et, benzene, 23 °C; (n) TBHP, (+)-DET, Ti(O*i*-Pr)$_4$, MS4A, CH_2Cl_2, −25 °C; (o) PivCl, pyridine, DMAP, CH_2Cl_2, 0 °C; (p) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C.

give **9** (91%). After the TBS group was removed from **9**, the resulting dihydroxy epoxide was cyclized with CSA to afford **10** (80%), which was transformed to **11** (54%) by a four-step process [(i) one-pot selective protection of the primary and secondary hydroxy groups, (ii) detachment of the Piv group, (iii) Dess–Martin oxidation,[9] and (iv) Wittig methylenation]. Intermediate E-ring **15** for **2b** was also synthesized from **7** via trans-epoxide **13**. After conversion of **7** to *E*-allyl alcohol **12** (81%) via Wittig reaction followed by DIBAH reduction, **13** was prepared by asymmetric epoxidation using (+)-DET (85%).[8] Transformation of **13** to **15** (overall yield 30%) was performed similarly to that of **9** to **11**.

Next, DE-ring models **2a** and **2b** were synthesized from **11** and **15**, respectively, via a process which included Ireland–Claisen rearrangement and ring-closing olefin metathesis (RCM) (Scheme 2).[10] Deprotection of **11** followed by reaction with bromoacetic acid afforded **16**, which was subjected to condensation with (*S*)-**17** and subsequent partial hydrogenation to give **18** (67% from **11**). Treatment of **18** with LHMDS in the presence of $MeSiCl_3$[11] at −78 °C followed by warming to ambient temperature induced the Ireland–Claisen rearrangement, and **19** was isolated (93%) after methylation with diazomethane. Diene **19** was transformed to **2a** through RCM with



Scheme 2. Reagents and conditions: (a) TBAF, THF, 23 °C; (b) NaH, *t*-BuOK, bromoacetic acid, THF, 23 °C; (c) (*S*)-**17**, EDCI·HCl, DMAP, CH_2Cl_2, 23 °C; (d) H_2, Lindlar cat., EtOH-0.5% quinoline in hexane (10:1.3, v/v); (e) LHMDS, $MeSiCl_3$, THF, −78 °C, then 23 °C; (f) CH_2N_2, Et_2O, 0 °C; (g) $(H_2IMes)(PCy_3)Cl_2RuCHPh$, CH_2Cl_2 (3 mM of substrate), 23 °C; (h) $LiAlH_4$, Et_2O, −20 °C; (i) (*R*)-**17**, EDCI·HCl, DMAP, CH_2Cl_2, 23 °C.



Scheme 3. Reagents and conditions: (a) **2a** or **2b**, DCC, DMAP, CH_2Cl_2, 23 °C; (b) TBAF, THF, 23 °C; (c) DMPI, CH_2Cl_2, 23 °C; (d) DDQ, CH_2Cl_2–H_2O (10:1), 23 °C; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O (3.5:1), 23 °C; (f) 2,4,6-trichlorobenzoyl chloride, Et_3N, 23 °C, then DMAP, toluene (5 mM of substrate), 60 °C.

second-generation Grubbs' catalyst[12] followed by reduction of the ester group (80%). Model **2b** was synthesized from **15** via the same process as above except that (*R*)-**17** was employed in the condensation step (overall yield 68%).

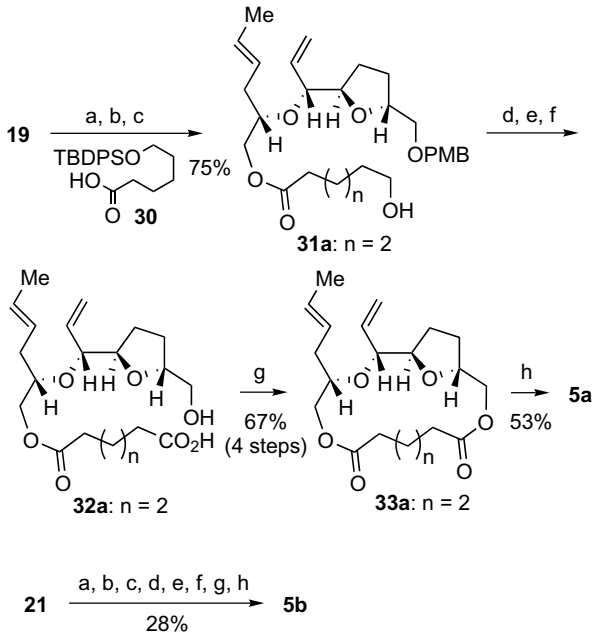
Both model compounds **2a** and **2b** showed an NOE enhancement between H16 and H20 and an absence of NOE between H21 and H24 in accordance with the reported data of **1**. However, both the models also displayed different values of $J_{H20–H21}$ (**2a**: 5.9 Hz, **2b**: 6.6 Hz) from that of **1**, and the relative stereochemistry of the DE-ring of **1** could not be confirmed at this stage. This disappointing result was attributed to the absence of a macrocyclic ring in the models. Therefore, macrocyclic models **3**–**5a**,**b** were synthesized for more precise stereochemical assessment of the DE-ring of **1**.

DE-ring models **2a** and **2b** were successfully transformed to the corresponding macrocyclic models **3**–**4a** and **3**–**4b** through a common six-step process illustrated in Scheme 3. For example, DE-ring model **2a** was initially condensed with carboxylic acid **22** (98%), and the resulting ester **24a** was subjected to a process including removal of the TBDPS group, Dess–Martin oxidation,[9] and PMB deprotection to produce hydroxyaldehyde **26a** (67%), which was then converted to **3a** (69%) by Pinnick oxidation[13] and Yamaguchi lactonization.[14] Macrocyclic models **3b**, **4a**, and **4b** were similarly obtained in 50% (from **2b**), 32% (from **2a**), and 9% overall yield (from **2b**), respectively.

Since 16-membered cyclic models **5a**,**b** could not be prepared from **2a**,**b** by the above route, we employed their alternative synthesis from **19** and **21** (Scheme 4).[15] Ester **19** was first reduced with $LiAlH_4$, and the resulting alcohol was converted to **31a** (75%) via esterification with **30** and TBDPS deprotection. Dess–Martin oxidation[9] of **31a** followed by PMB deprotection and Pinnick oxidation[13] gave **32a**, which was lactonized by Yamaguchi's method[14] to produce **33a** (67% from **31a**). Diene **33a** was cyclized with second-generation Grubbs' catalyst[12] to furnish **5a** (53%). Model **5b** was also synthesized from **21** in the same way (overall 28%). Since **5a** and **5b** were obtained as crystals, their stereochemistry was confirmed by X-ray crystallographic analysis (Fig. 4).[16]

The $J_{H20–H21}$ values of models **2**–**5a**,**b** are listed in Table 1. While the $J_{H20–H21}$ values of non-macrocyclic models **2a**,**b** are both around 6 Hz, each $J_{H20–H21}$ of the **a**-series macrocyclic models is clearly larger (5.4–7.5 Hz) than that of the corresponding **b**-series model (2.6–3.6 Hz). Therefore, the $J_{H20–H21}$ values of **a**-series models replicated that of **1** better than the **b**-series models. It is also notable that, as the ring size of the models decreased, the difference of $J_{H20–H21}$ between **a**- and **b**-series models increased and the discrepancy of $J_{H20–H21}$ between an **a**-series model and **1** was reduced.[17]

In the following paragraphs, we discuss the effect of the relative stereochemistry of the macrocyclic models on the size of $J_{H20–H21}$ values. Because a measured value of $^3J_{H–H}$ in a flexible molecule results from a population weighted



Scheme 4. Reagents and conditions: (a) $LiAlH_4$, Et_2O, −20 °C; (b) **30**, DCC, DMAP, CH_2Cl_2, 23 °C; (c) TBAF, THF, 23 °C; (d) DMPI, CH_2Cl_2, 23 °C; (e) DDQ, CH_2Cl_2–H_2O (20:1), 23 °C; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O (3.5:1); (g) 2,4,6-trichlorobenzoyl chloride, Et_3N, 23 °C, then DMAP, toluene (5 mM of substrate), 60 °C; (h) $(H_2IMes)(PCy_3)Cl_2RuCHPh$, CH_2Cl_2, reflux.

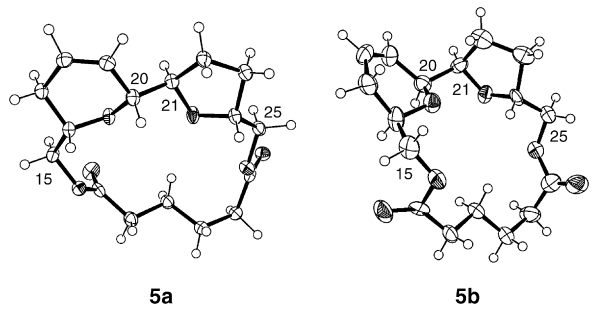


Fig. 4. ORTEP diagrams of **5a** and **5b**.

Table 1

	a-Series $J_{H20–H21}$	b-Series $J_{H20–H21}$
Non-macrocyclic models	**2a**: 5.9 Hz[a]	**2b**: 6.6 Hz[b]
Macrocyclic models		
$n = 6$	**3a**: 5.4 Hz[c]	**3b**: 3.6 Hz[b]
$n = 4$	**4a**: 6.1 Hz[d]	**4b**: 3.3 Hz[a]
$n = 2$	**5a**: 7.5 Hz[b]	**5b**: 2.6 Hz[b]
Goniodomin A (**1**)	9.4 Hz[b]	

[a] In $CDCl_3$.
[b] In C_6D_6.
[c] In CD_3CN.
[d] In C_5ND_5.

average of $^3J_{H–H}$ values over all conformers, difference of the stereoisomeric macrocyclic models in conformer population ratio should be considered.

There are three basic conformers around the C20–C21 bond in each DE-ring model, namely, two H20,H21-*gauche* and one H20,H21-*anti* conformers.[18] From the ORTEP diagrams (Fig. 4), it is clear that the conformation of macrocyclic model **5a** in the crystal form assumes an H20,H21-*anti* relationship, and that of **5b** takes on an H20,H21-*gauche* relationship. The conformational preference is attributed to the distance between C15 and C25. When the dicarboxylate chain is of limited length, the C15–C25 distance is kept to a minimum (6.982 Å in **5a** and 6.101 Å in **5b**). On the other hand, conformers with a longer C15–C25 distance would be energetically unfavorable in such a situation. Therefore, an H20,H21-*gauche* conformer of **5a** and an H20,H21-*anti*-conformer of **5b**, in which the estimated C15–C25 distances are 8.27 Å and 8.08 Å, respectively, would constitute only negligible fractions of the total conformer population.[19]

The measured $J_{H20–H21}$ values in each of **1**, non-macrocyclic models **2a**,**b**, and macrocyclic models **3**–**5a**,**b** result from a population weighted average of $J_{H20–H21}$ values for all conformers around the C20–C21 bond in each compound. It is predicted from the Karplus relationship[20] that the $J_{H20-H21}$ value of the H20,H21-*gauche* conformer is small (0–3 Hz) and that of the H20,H21-*anti* conformer is large (7–10 Hz).[21,22] Hence, the negligible contribution of the H20,H21-*gauche* conformer of the **a**-series macrocyclic models would make the observed $J_{H20–H21}$ value large, while the minor population of the H20,H21-*anti* conformer of the **b**-series models would reduce the observed $J_{H20–H21}$ value. The observed medium values of $J_{H20–H21}$ of **2a** and **2b** are attributed to a relatively uniform population distribution of the three basic conformers. Thus, it is reasonable to assume that the relative stereochemistry of macrocyclic DE-ring models is reflected in the size of their $J_{H20–H21}$ values.

Goniodomin A (**1**) has a large $J_{H20–H21}$ value (9.4 Hz). This suggests a high incidence of an H20,H21-*anti* conformer due to the restricted C20–C21 bond rotation, even though the DE-ring of **1** is connected with a long chain (at least 15 atoms) between C15 and C25. This is not surprising, because the chain is inflexible. It includes only eight rotatable bonds and several rigid parts [an oxane (A-ring), a spirocyclic acetal (BC-ring), an ester group, and a cis double bond (C29=C30)]. Therefore, the chain would keep the distance between C15 and C25 to a minimum, and the DE-ring would adopt the H20,H21-*anti* conformer, which shows a large $J_{H20–H21}$, with high occurrence. From consideration of the macrocyclic models, it is clear that the H20,H21-*anti* conformer of the DE-ring with a shorter C15–C25 distance would be included in a compound that has the **a**-series stereochemistry (**1a**). Thus, *it is predicted that the relative stereochemistry of the DE-ring of* **1** *is the same as that of the* **a**-*series models* (Fig. 5).

In conclusion, two stereoisomeric series of non-macrocyclic and macrocyclic DE-ring model compounds of goniodomin A (**1**) were synthesized, and the natural relative stereochemistry of the DE-ring (**1a**) was predicted by

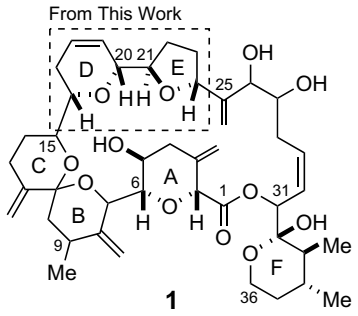


Fig. 5. Predicted partial relative stereochemistry of **1**.

NMR comparison of **1** with these model compounds. Further studies toward determination of the full absolute configuration of **1** by total synthesis are in progress in this laboratory.

Acknowledgments

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15. Although the precursor secoic acids for **5a**,**b** having an intact DE-ring could be synthesized from **2a** and **2b**, the final macrocyclization step gave only oligomeric side products.
16. *Crystal data of* **5a**: $C_{17}H_{24}O_6$, M 324.37, orthorhombic $P2_12_12_1$ (No. 19), $a = 5.140(1)$ Å, $b = 16.891(4)$ Å, $c = 18.332(5)$ Å, $V = 1591.7(7)$ Å^3, D_c $(Z = 4) = 1.354$ g/cm^3, $T = 153$ K, $\mu = 1.02$ cm^{-1}. The final R value is 0.034 for 2436 independent reflections with $I > 2\sigma I$ and 209 parameters. Crystal data of **5b**: $C_{17}H_{24}O_6$, M 324.37, orthorhombic $P2_12_12_1$ (No. 19), $a = 5.249(3)$ Å, $b = 9.302(5)$ Å, $c = 34.16(2)$ Å, $V = 1667.7(1)$ Å^3, D_c $(Z = 4) = 1.292$ g/cm^3, $T = 153$ K, $\mu = 0.97$ cm^{-1}. The final R value is 0.068 for 951 independent reflections with $I > 3\sigma I$ and 209 parameters. Crystallographic data (excluding structure factors) of **5a** and **5b** have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 664790 and 664791, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033, e-mail: deposit@ccdc.cam.ac.uk, or web: http://www.ccdc.cam.ac.uk/].
17. There is still a slight discrepancy between the $J_{H20–H21}$ values of model **5a** (7.5 Hz) and **1** (9.4 Hz). The discrepancy may be attributable to the difference in the rigidity between the simple dicarboxylate chain of the model and the complex chain of **1** which includes several inflexible parts, such as an oxane and a spirocyclic acetal.
18. The terms 'H20,H21-*gauche*' and 'H20,H21-*anti*' are used for convenience. 'H20,H21-*gauche*' and 'H20,H21-*anti*' indicate that the conformational relationship between H20 and H21 is *gauche* or *anti*, respectively.
19. The C15–C25 distances of the H20,H21-*gauche* conformer of **5a** and the H20,H21-*anti* conformer of **5b** were estimated from simple Chem3D models based on the X-ray coordinates of **5a** and **5b**. Each model conformer was obtained as follows: the dicarboxylate chain was removed from each coordinate, and the C20–C21 bond was simply rotated until the desired conformer was given. The remaining H20,H21-*gauche* conformers of **5a** and **5b** are expected to exist with relatively high conformer population due to the relatively short C15–C25 distances approximated (6.79 Å in **5a** and 6.99 Å in **5b**).
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