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Enhancing Intermolecular Benzoyl-Transfer Reactivity in Crystals by Growing a "Reactive" Metastable Polymorph by Using a Chiral Additive

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Abstract: Racemic 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoacetate, which normally crystallizes in a monoclinic form (form I, space group $P2_1/n$) could be persuaded to crystallize out as a metastable polymorph (form II, space group $C2/c$) by using a small amount of either D- or L- 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate as an additive in the crystallization medium. The structurally similar enantiomeric additive was chosen by the scrutiny of previous experimental results on the crystallization of racemic 2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoacetate.
Form II crystals can be thermally transformed to form I crystals at about 145 °C. The relative organization of the molecules in these dimorphs vary slightly in terms of the helical assembly of molecules, that is, electrophile (El)···nucleophile (Nu) and C–H···π interactions, but these minor variations have a profound effect on the facility and specificity of benzoyl-group-transfer reactivity in the two crystal forms. While form II crystals undergo a clean intermolecular benzoyl-group-transfer reaction, form I crystals are less reactive and undergo non-specific benzoyl-group transfer leading to a mixture of products. The role played by the additive in fine-tuning small changes that are required in the molecular packing opens up the possibility of creating new polymorphs that show varied physical and chemical properties. Crystals of D-2,6-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate (additive) did not show facile benzoyl-group-transfer reactivity (in contrast to the corresponding racemic compound) due to the lack of proper juxtaposition and assembly of molecules.

Keywords: acylation · carbohydrates · crystal growth · cyclitols · solid-state reactions

Introduction

The study of organic reactions in molecular solids and crystals has emerged as a frontier area of research in the recent past. Although reactions in molecular crystals are less common than reactions in the gas phase or in solution, the degree of (regio- and/or stereo-) control exerted by the crystalline state is often comparable to that observed in enzymatic processes.[1] This is essentially due to the "pre-organization" of the reacting molecules in crystals and the inability of the reactant molecules to freely move in the crystalline state, in contrast to that in the gaseous and solution states. Wide-ranging areas of interest in organic solid-state chemistry include topochemical dimerization or polymerization that involves addition to C=C double bonds,[2] group-transfer reactions in crystals,[3] mechanistic organic photochemistry,[4] generation of chiral products from achiral reactant molecules in crystalline solids,[5] crystal-to-crystal reactions[5c,6] as tools for the development of green chemistry,[7] reactions in co-crystals[8] and inclusion crystals,[9] control of reactivity in the solid state by using linear molecular templates,[10] reaction between co-crystals,[11] asymmetric synthesis in inclusion crystals by using chiral hosts,[5c,6a,12] solid-state reaction kinetics,[13] prediction of reactivity by using computational methods,[14] mechanochemical reactions[3g] and the development of functional materials.[10c] The rationalization, prediction and control of structure and properties of organic solid phases is difficult due to the complex nature of weak intermolecular non-covalent bonding.[15] Hence, the

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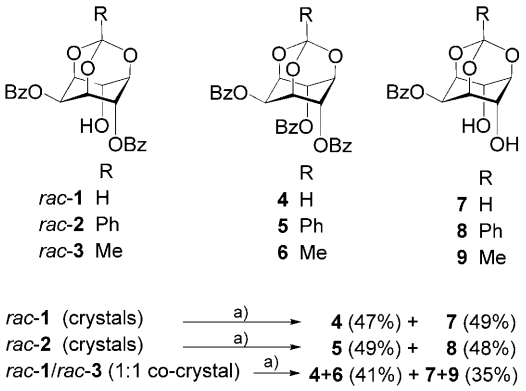
key to carrying out solid-phase bimolecular reactions is to obtain crystals in which the reacting molecules are arranged with the required precise distances and relative orientation between potential reaction centres or to facilitate the interaction of reagent molecules with substrate molecules in crystals without disturbing the crystal lattice. Engineering of molecular crystals with desired physical or chemical properties has been approached by attempts to control polymorphism,[16] attempts to grow and stabilize metastable polymorphs,[17] attempts to gain control over the non-covalent self-assembly of molecules[10d,18] and the use of templates[19] and additives[20] for crystallization. Achieving the seemingly Utopian possibility of breaking and making covalent bonds in molecular crystals in a predictable manner requires the identification of suitable reactions, establishing their generality and developing mechanistic models to engineer other crystals that exhibit the desired reactions. We have been investigating acyl-transfer reactions in crystals (Scheme 1) over the last few years[21] with these goals in mind. Although acyl-transfer reactions have been investigated[22] for more than a century in living cells in the laboratory and in industry, their occurrence in the crystalline state was discovered in our laboratory.[21a]



Scheme 1. Solid-state transesterification reactions in crystals of *myo*-inositol orthoester derivatives. a) Na_2CO_3, heat.

A comparison of the structure of crystals[21] in which intermolecular acyl-transfer was facile and not so facile revealed that the following features were necessary in the crystal for facile acyl-transfer reactions: 1) the properly juxtaposed reacting pair of molecules has to make a "reaction channel" by helically self-assembling itself around a crystallographic screw axis for the propagation of the intermolecular benzoyl group-transfer reaction in crystals; 2) good electrophile (El)···nucleophile (Nu) geometry;[23] and 3) C–H···π interactions.[24] These interactions made by the migrating benzoyl group appeared to augment the facility of the intermolecular benzoyl-group transfer. A crystal form (herein referred to as form I—space group $P2_1/n$) of the orthoacetate derivative *rac*-**3** had the molecular pre-organization grossly satisfying all the above criteria, but the acyl-transfer reactivity in form I crystals was very low yielding and non-specific.[21b] The present work reports how the acyl-transfer reactivity was enhanced by the formation of a new highly reactive metastable crystal form of *rac*-**3** by using a trace of an analogous chiral additive (an enantiomer of the orthoformate *rac*-**1**) in the crystallization medium.[25]

Results and Discussion

The reactive centrosymmetric crystals in which the benzoyl-group-transfer reaction (Scheme 1)[21] proceeded with high facility, consistently reinforced a pattern of helical molecular assembly (see the Supporting Information) of molecules with the same configuration (*R* or *S*).[21,26] In these crystals, the benzoyl-group-transfer reaction took place among molecules with the same absolute configuration (i.e., either from *R* to *R* or from *S* to *S* enantiomers) along the crystallographic 2_1 screw axis. Experimental evidence for this came from the reactive co-crystal[21b] *rac*-**1**•*rac*-**3** (1:1) formed from the reactive orthoformate *rac*-**1** and the less reactive orthoacetate *rac*-**3**. In this co-crystal, the asymmetric unit consisted of one molecule each of *rac*-**1** and *rac*-**3** containing the same configuration and related by a non-crystallographic 2_1-screw axis. This asymmetric unit then arranged itself helically around the 2_1 screw axis in a monoclinic space group *Cc* providing a (almost) continuous helical channel for the benzoyl-group-transfer reaction to occur.[21b] We noted that co-crystals *rac*-**1**•*rac*-**3** contained only *RR* and *SS* pairs of dibenzoates *rac*-**1** and *rac*-**3** (of the four possible diastereomeric pairs). These observations prompted us to attempt crystallization of *rac*-**3** in the presence of an enantiomer **1** or *ent*-**1**. Considering the similarities in the arrangement of molecules in crystals of *rac*-**1**, *rac*-**3** (form I) and *rac*-**1**•*rac*-**3** as well as similarities in the molecular structure and conformation of *rac*-**1**, *rac*-**3** and enantiomer *ent*-**1** (or **1**) we expected one of the two following outcomes in the crystallization experiment: 1) resolution of *rac*-**3** by formation of co-crystals consisting of one of the enantiomers in *rac*-**3** and *ent*-**1** (or **1**)[27] or 2) formation of a new polymorph of *rac*-**3**.[17] We envisaged the latter possibility since there is precedent in the literature that additives that mimic the conformation of molecules in stable crystal structures lead to the formation of polymorphs (Figure 1).

The enantiomeric dibenzoates **1** and *ent*-**1** were prepared from the enantiomeric ditosylates **10** and *ent*-**10**[28] as shown in Scheme 2. Crystallization of dibenzoates **1** and *ent*-**1** from chloroform/light petroleum gave crystals suitable for single-crystal X-ray diffraction studies. We also prepared D-6-*O*- and D-4-*O*-benzyl-*myo*-inositols **14** and *ent*-**14**, which are precursors for the preparation of enantiomeric *myo*-inositol-1,2,3,4,5-pentakisphosphates. The benzyl ethers **14** and *ent*-**14** have earlier been prepared from *myo*-inositol[29] as well as from benzoquinone.[30] The overall yield of enantiomeric benzyl ethers **14** and *ent*-**14** in these reported procedures is in the range of 3–17%. The method shown in Scheme 2 provides **14** and *ent*-**14** in an overall yield of ≈25%, which is better than the previously reported proce-

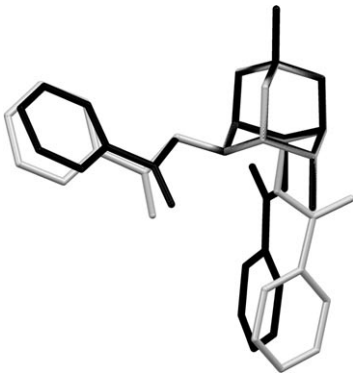
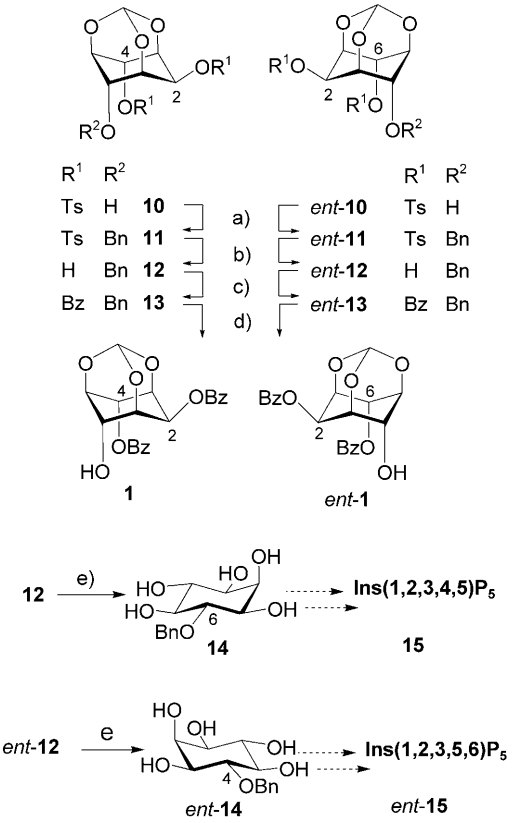


Figure 1. Overlap diagram of molecules present in crystals of *ent*-**1** (light grey) and *rac*-**3** (black).



Scheme 2. Preparation of enantiomeric *myo*-inositol derivatives. a) DMF, BnBr, NaH, 0 °C–RT, 30 min, 94–96 %; b) NaOMe, MeOH, reflux, 12 h, 92–98 %; c) pyridine, BzCl, RT, 20 h, 96–98 %; d) ethyl acetate/methanol, $Pd(OH)_2/C$, H_2 (55 psi), RT, 6 h, 94–96 %; e) TFA/H_2O (4:1 v/v), RT, 24 h, 84–87 %. TFA = trifluoroacetic acid.

dures. This procedure can also be adopted to prepare many other 4-*O*-substituted *myo*-inositol derivatives; such derivatives are valuable tools for the study of inositol binding proteins.[31] We had earlier shown[28,32] that inositol derivatives can be obtained in very good yields from *myo*-inositol-1,3,5-orthoformate by using sulfonate groups for the protection of its hydroxyl groups.

The dibenzoate *rac*-**3** crystallized (Table 1) as form I crystals from most organic solvents, whereas it gave a 1:1 co-crystal *rac*-**1**•*rac*-**3** on crystallization with *rac*-**1** from a chloroform/light petroleum mixture.[21b] Crystallization of *rac*-**3** in the presence of *ent*-**1** (or **1**) gave a new polymorph (form II) of *rac*-**3** (Figure 2B). The actual outcome of the experiment was dependent on the molar ratio *ent*-**1**/*rac*-**3**; use of smaller amounts of *ent*-**1** in the crystallization medium led to concomitant formation of both the polymorphs (Table 1, entry 5) of *rac*-**3**, whereas the presence of a larger amount of *ent*-**1** prevented crystal formation completely (entry 6). Repeated attempts to obtain co-crystals from *rac*-**3** and either **1** or *ent*-**1** were not successful. Form II crystals could be thermally transformed irreversibly to form I crystals above 145 °C as revealed by thermal analysis (Figure 3) and X-ray crystallography.

Table 1. Results of the crystallization of *rac*-**3** in the presence of its orthoformate analogues.

Entry[a]	Molar ratio of orthoesters	Result
1	*rac*-**3**	form I
2	*rac*-**1**/*rac*-**3** (1:1)	*rac*-**1**•*rac*-**3**[b]
3	*ent*-**1**/*rac*-**3** (1:1)	form II
4	*ent*-**1**/*rac*-**3** (1:9)	form II
5	*ent*-**1**/*rac*-**3** (1:18)	form I and II
6	*ent*-**1**/*rac*-**3** (9:1)	amorphous solid

[a] Solvent system for all entries: chloroform/light petroleum (vapour diffusion method); [b] 1:1 co-crystals were obtained irrespective of the ratio of *rac*-**1** and *rac*-**3** present in solution.[21b]

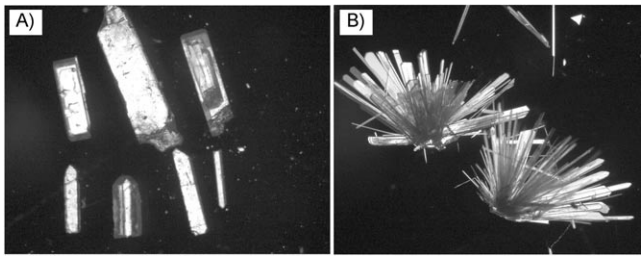


Figure 2. Photomicrographs of form I (A) and II (B) crystals of *rac*-**3**.

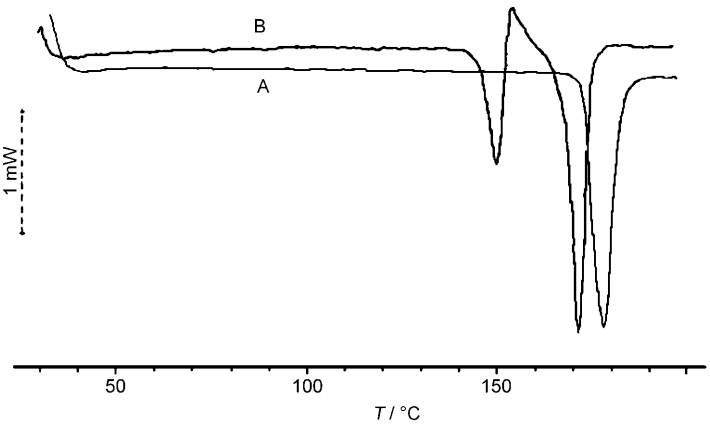


Figure 3. Thermal analysis (DSC) of form I (A) and II (B) crystals of *rac*-**3**.

The X-ray diffraction data obtained on the form II crystals (space group $C2/c$) of *rac*-**3** revealed them to be isostructural to the co-crystals *rac*-**1**·*rac*-**3** (space group Cc). Similarities were observed in terms of O–H···O and El···Nu interactions. In form II crystals of *rac*-**3**, molecules containing the same configuration assembled helically around the crystallographic 2_1 screw axis, with the geometrical parameters (O–H···O, El···Nu and C–H···π interactions) favourable for the intermolecular benzoyl-group-transfer reaction (Figure 4 and Tables 2 and 3). The conformational differences (Figure 5) between the two forms at the singular molecular level appears to have contributed significantly to the improvement in the El···Nu and C–H···π interactions in form II crystals (Figure 4).

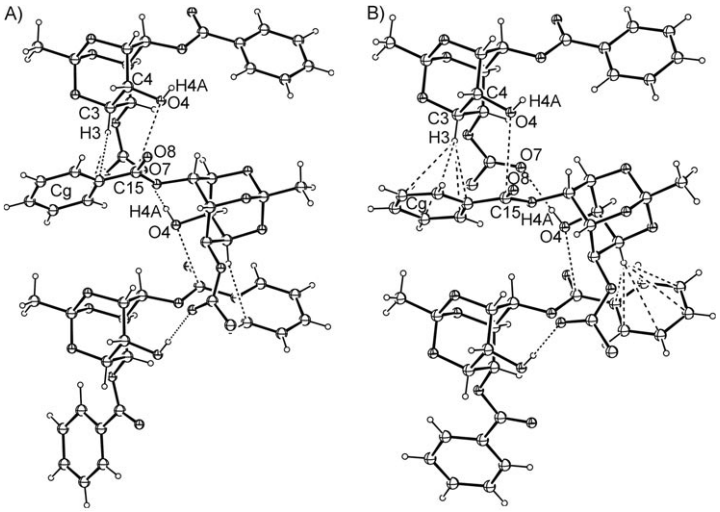


Figure 4. Comparison of El···Nu geometry and allied weak interactions in form I (A) and II (B) crystals of *rac*-**3**.

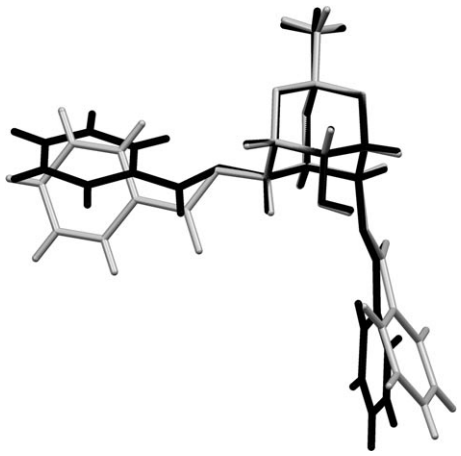
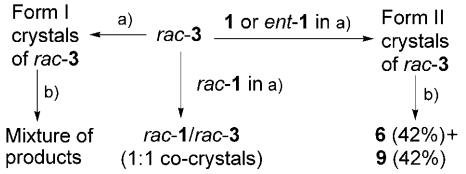


Figure 5. Overlap diagram of molecules present in crystals of form I (black) and II (light grey) of *rac*-**3**.

Since the crystal structural parameters that govern benzoyl-transfer reactions and molecular organization were good in form II crystals of *rac*-**3**, we predicted the occurrence of facile intermolecular benzoyl-transfer reactivity in these crystals. Indeed, heating them at 115 °C with solid sodium carbonate yielded the tribenzoate **6** and the diol **9** in very good yields (Scheme 3). The temperature of the reaction



Scheme 3. Acyl-transfer reactions in crystals of *rac*-**3**. a) Chloroform/light petroleum; b) Na_2CO_3, 115 °C.

Table 2. Hydrogen-bonding parameters in crystals of *rac*-**3** and *ent*-**1**.

	D–H···A	H···A [Å]	D···A [Å]	D–H···A [°]
form I	O(4)–H(4 A)···O(7)[a]	1.93	2.775(2)	175
	C(3)–H(3)···Cg(1)[b]	3.67	4.472	142
form II	O(4)–H(4 A)···O(7)[c]	2.00	2.822(3)	176
	C(3)–H(3)···Cg(1)[d]	2.62	3.582	167
ent-**1**	O(4)-H(4 A)···O(8)[e]	2.02(2)	2.788(2)	172(2)
	C(5)-H(5)···Cg(1)[f]	3.265	4.086	139

Symmetry code: [a] $1.5-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$; [b] $1.5-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$; [c] $\frac{1}{2}-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$; [d] $\frac{1}{2}-x$, $\frac{1}{2}+y$, $\frac{1}{2}-z$; [e] $-\frac{1}{2}+x$, $-\frac{1}{2}-y$, $-z$; [f] $-\frac{1}{2}+x$, $-\frac{1}{2}-y$, $-z$.

Table 3. Geometry of the reacting groups (El···Nu) in crystals of *rac*-**3** and *ent*-**1**.

Distance [Å]/angle [°]	form I	form II	*ent*-**1**
C15···O4	3.299(2)[a]	3.135(4) [b]	4.484(2)[c]
∢O4···C15–O8	84.01	87.63	50.3(2)
∢C4–O4···C15	97.20	116.46	157.3(2)
∢H4A–O4···C15	105.8	114.05	51.5(1)

Symmetry code: [a] $1.5-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$; [b] $\frac{1}{2}-x$, $-\frac{1}{2}+y$, $\frac{1}{2}-z$; [c] $-\frac{1}{2}+x$, $-\frac{1}{2}-y$, $-z$.

mixture was maintained well below the form I to form II phase transition temperature of 145 °C. Form I crystals when subjected to similar reaction conditions (at 115 °C) gave several products due to inefficient benzoyl-group transfer.[21b]

The solid-state reactivity of this new polymorph (from II) was as good as in crystals of *rac*-**1** and *rac*-**2** (Scheme 1) investigated earlier.[21] This finding reinforces the importance of the proposed[21] topochemical criterion and overall molecular organization responsible for the efficient intermolecular acyl-transfer reaction in crystals. It is very intriguing that the presence of a minor amount of an enantiomer (either **1** or *ent*-**1**) of the orthoformate (without actually being a part of the crystal) in the crystallization medium can coax molecules of *rac*-**3** to pack in a manner conducive to the benzoyl-transfer reaction in crystals. We had observed earlier[21b] that half an equivalent of the racemic orthoformate *rac*-**1** (by being a part of the co-crystal with *rac*-**3**) could coax the molecules of *rac*-**3** to efficiently participate in the benzoyl-transfer reaction.

Although nucleation is a complex phenomenon, attempts are made to explain the growth of the reactive polymorph

form II of *rac*-**3**. A tentative mechanism for the formation of form II crystals of *rac*-**3** can be depicted as follows. In principle, the additive *ent*-**1** (or **1**) can play one of two roles during the crystallization of *rac*-**3**. Either *ent*-**1** can just inhibit the formation of form I crystals (and form II crystals grow on their own) or *ent*-**1** can facilitate the growth of form II crystals. Although the former possibility is supported by the fact that additives, which mimic the conformation of molecules in the thermodynamically stable crystal structure, can kinetically stabilize a metastable polymorph,[17] the latter possibility cannot be ruled out. The basis for this is derived from the results of the crystallization experiments carried out on *myo*-inositol orthoester derivatives, including the formation of a co-crystal *rac*-**1**•*rac*-**3** with the same unit-cell parameters as form II crystals of *rac*-**3**.[21b] Figure 6 shows the similarities in the arrangement of molecules in these two crystals.

Since the form II crystals undergo thermal transformation to form I crystals before melting, it can be concluded that form I crystals are thermodynamically stable, whereas form II crystals are a metastable form. As observed in crystallization experiments (Table 1) the appearance of form II crystals was preferred over that of form I crystals in the presence of *ent*-**1** (or **1**). Molecular organization in crystals of *rac*-**1** is known to bring about neat benzoyl-transfer reactivity.[21b] The nucleation properties of *rac*-**1** leading to this molecular arrangement are obviously very predominant, because the presence of 50% of *rac*-**1** with *rac*-**3** in co-crystals *rac*-**1**•*rac*-**3** resembled *rac*-**1** organization and not that of form I crystals of *rac*-**3.** This suggests that this inherent property (crystallographic gene!?) of *rac*-**1** leads to the nucleation of form II crystals of *rac*-**3**. Although the enantiomer *ent*-**1** is present at 10% concentration, it is enough to induce the helical assembly to grow in the "right" way, biasing the entire nucleation to yield the reactive form II. This possibility for the growth of form II crystals is shown as a cartoon in Figure 7.

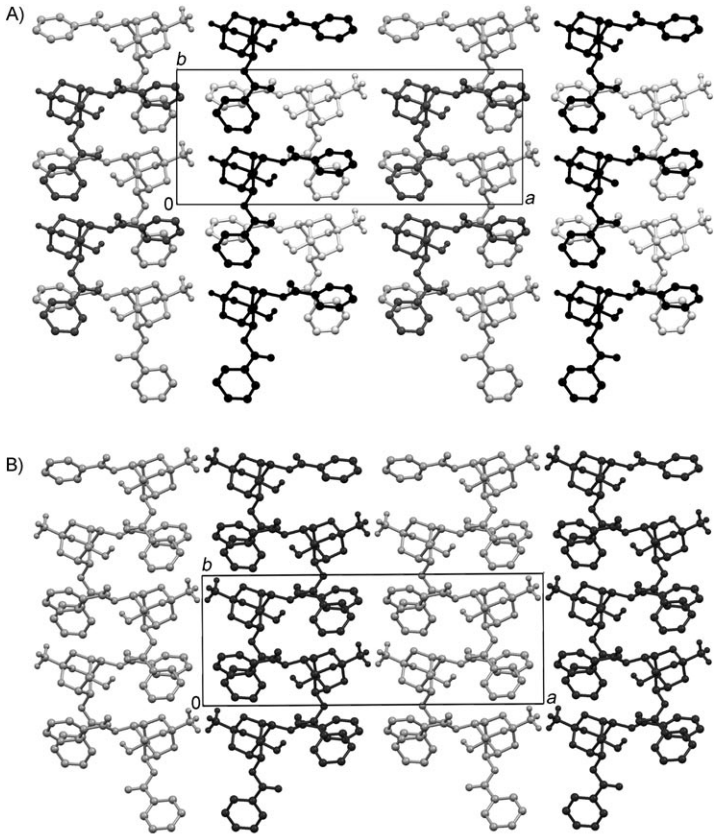


Figure 6. Comparison of the molecular organization in A) co-crystal *rac*-**1**•*rac*-**3** and B) form II of *rac*-**3** viewed down the *c* axis.

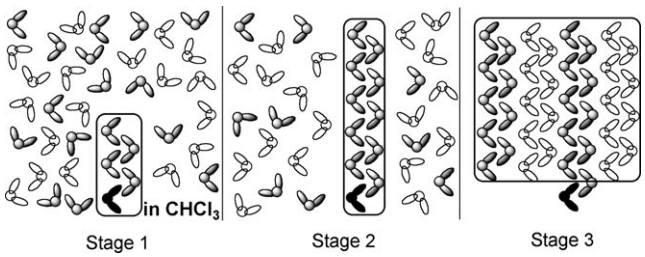


Figure 7. Stage 1: Nucleation of the form II crystal (of *rac*-**3**), with the aid of *ent*-**1** (or **1**), by the aggregation of molecules of *rac*-**3** with the same relative configuration as *ent*-**1** (or **1**). This molecular assembly is suggested to be isostructural to that of the co-crystal *rac*-**1**•*rac*-**3**. Stage 2: Growth of the helix along the screw axis, by assembly of molecules of *rac*-**3** with the same configuration (D or L). Stage 3: Complementary helical assembly (helix constituted by plain molecules) of molecules of *rac*-**3** leading to complete crystal formation and its stabilization. Filled molecules: **1** or *ent*-**1**; plain molecules: one of the enantiomers of *rac*-**3**; shaded molecules: enantiomer of *rac*-**3** with a configuration opposite to that of the plain molecule.

Availability of crystals of *ent*-**1** also allowed us to address another question. Since we had observed the formation of the helical assembly of molecules with the same chirality in crystals of *rac*-**1** (amounting to separation of molecules along the screw axis in crystals of *rac*-**1**), we wondered what would be the molecular organization in crystals if enantiomer *ent*-**1** (or **1**) was crystallized separately? Enantiomer *ent*-**1** crystallized in orthorhombic space group $P2_12_12_1$ and contained a helical organization of molecules along all the three axes (Figure 8), but none had the molecular assembly comparable to that observed in crystals of *rac*-**1** (Table 3). The enatiomer *ent*-**1** did not undergo clean transesterification reactions in their crystals, which is consistent with their crystal structure, which lacks good El···Nu interactions (Table 3). Hence it appears that interhelical interactions present in crystals of *rac*-**1** are necessary for the formation of the helical assembly (of these dibenzoate molecules) capable of initiating and sustaining intermolecular benzoyl-transfer reactions in crystals.

Conclusion

The role played by the chiral additive in fine-tuning small changes required in the molecular packing in crystals opens

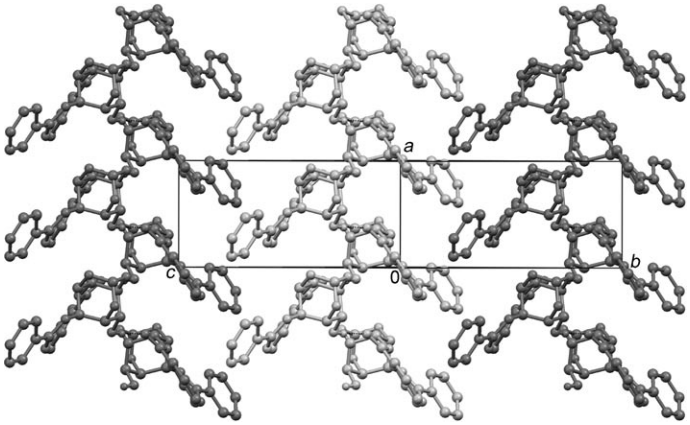


Figure 8. Helical assembly of molecules in crystals of *ent*-**1** viewed diagonal to the *bc* plane.

up possibilities of creating new polymorphs of a compound containing varied physical and chemical properties.[33] It is pertinent to mention that the metastable form II crystals of *rac*-**3** was not obtained by random screening of additives for crystallization experiments, but rather by consideration of previous experimental results for the selection of the additive. A comparison of structure and reactivity of form I and II crystals shows that, for neat intermolecular benzoyl-group-transfer reactions to occur in the solid state, the geometry and organization of the molecules as depicted in Figure 4 is very crucial. It is interesting and important to note that the presence of a racemic substance and its enantiomer can have a profoundly different influence on the outcome of the crystallization of substances. Based on these observations, the possibility of designing and constructing other molecular systems that show "acyl-transfer activities" in crystals is being explored in our laboratory.

Experimental Section

General: All the solvents were purified according to literature procedures[34] before use. 60% dispersion of sodium hydride in mineral oil was used for *O*-alkylation reactions. TLC was performed on E. Merck precoated 60 F_{254} plates and the spots were rendered visible either by shining UV light or by charring the plates with concd H_2SO_4. Workup implies the washing of the organic layer successively with water, dilute HCl (≈2%), water, saturated sodium bicarbonate solution, water and then brine. Column chromatographic separations were carried out on silica gel (60–120 mesh or 230–400 mesh) with the solvent system as mentioned in experimental procedures. TLC R_f values reported are with the same eluent as that used in column chromatography. The compounds previously reported in the literature were characterized by comparison of their melting points and/or ^{1}H NMR spectra with reported data. All the asymmetrically substituted racemic *myo*-inositol derivatives (numbered with the prefix *rac*-) are represented in the schemes by one of the enantiomers without numbering of the inositol ring carbon atoms.

D-2,4-Di-*O*-tosyl-6-*O*-benzyl-*myo*-inositol-1,3,5-orthoformate (11): Sodium hydride (0.087 g, 2.18 mmol) was added to an ice-cooled solution of D-2,4-di-*O*-tosyl-*myo*-inositol-1,3,5-orthoformate (**10**, 0.951 g, 1.91 mmol) and benzyl bromide (0.34 mL, 2.86 mmol) in dry DMF (10 mL), and the reaction mixture was stirred at ambient temperature for 30 min. Excess of sodium hydride was quenched with ice and the solvent was removed under reduced pressure. The residue was worked up with dichloromethane and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure afforded a gummy residue. The crude product was purified by column chromatography (eluent: 25% ethyl acetate/light petroleum) to give **11** as a white solid (1.077 g, 96%). R_f=0.31; m.p. 76–78°C; $[\alpha]_D^{29}=-8.85$ (c=1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ=7.67–7.84 (m, 4H; Ar H), 7.21–7.38 (m, 9H; Ar H), 5.43 (d, 1H, J=1.3 Hz; HCO_3), 5.08 (dt, 1H, J=4.1, 1.7 Hz; Ins H), 4.92 (dt, 1H, J=3.27, 1.76 Hz; Ins H), 4.42–4.64 (q, 2H, J=11.6 Hz; CH_2), 4.33–4.41 (m, 1H; Ins H), 4.24 (dt, 1H, J=4.2, 1.6 Hz; Ins H), 4.12–4.20 (m, 1H; Ins H), 4.01–4.11 (m, 1H; Ins H), 2.47 (s, 3H; Me), 2.43 ppm (s, 3H; Me); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): δ=145.6 (C_{arom}), 145.3 (C_{arom}), 136.7 (C_{arom}), 132.7 (C_{arom}), 132.2 (C_{arom}), 130.0 (C_{arom}), 129.9 (C_{arom}), 128.3 (C_{arom}), 127.8 (C_{arom}), 127.7 (C_{arom}), 127.3 (C_{arom}), 102.4 (HCO_3), 72.2 (Ins C), 72.0 (Ins C), 71.2 (CH_2), 69.8 (Ins C), 69.6 (Ins C), 68.6 (Ins C), 67.0 (Ins C), 21.5 (CH_3), 21.4 ppm (CH_3); elemental analysis calcd (%) for $C_{28}H_{28}O_{10}S_2$: C 57.13, H 4.79, S 10.89; found: C 57.20, H 4.88, S 10.55%.

D-6-*O*-Benzyl-*myo*-inositol-1,3,5-orthoformate (12): A mixture of the ditosylate **11** (1.015 g, 1.72 mmol), sodium methoxide (0.931 g, 17.2 mmol) and dry methanol (10 mL) was refluxed for 12 h. The reaction mixture was allowed to cool to ambient temperature and methanol was removed under reduced pressure to give a gummy residue. The residue was purified by column chromatography (eluent: ethyl acetate/light petroleum 1:2) to give **12** as a gummy compound (0.445 g, 92%). R_f=0.28; $[\alpha]_D^{27}=-14.9$ (c=0.01 in ethanol) (lit.:[35] $[\alpha]_D^{25}=-16.6$ (c=1 in EtOH)); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ=7.28–7.45 (m, 5H; Ar H), 5.44 (d, 1H, J=1.3 Hz; HCO_3), 4.61–4.73 (q, 2H, J=11.6 Hz; CH_2), 3.39–4.45 (m, 2H; Ins H), 4.18–4.32 (m, 3H; Ins H), 4.09 (d, 1H, J=9.5 Hz; Ins H), 3.74 (d, 1H, J=10.2 Hz; OH), 3.21 ppm (d, 1H, J=11.2 Hz; OH); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): δ=135.8 (C_{arom}), 128.7 (C_{arom}), 128.6 (C_{arom}), 127.9 (C_{arom}), 102.5 (HCO_3), 74.6 (Ins C), 74.0 (Ins C), 72.8 (CH_2), 72.1 (Ins C), 67.7 (Ins C), 67.1 (Ins C), 60.4 ppm (Ins C); IR (neat): $\tilde{\nu}$=3300–3650 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{16}O_6$: C 59.99, H 5.75; found: C 59.84, H 5.84.

D-2,4-Di-*O*-benzoyl-6-*O*-benzyl-*myo*-inositol-1,3,5-orthoformate (13): Benzoyl chloride (1.053 g, 7.49 mmol) was added dropwise over a period of 10 min to an ice-cooled solution of the diol **12** (0.35 g, 1.25 mmol) and 4-dimethylaminopyridine (DMAP; 0.02 g) in dry pyridine (6 mL). The reaction mixture was stirred for 20 h at ambient temperature and then the pyridine was removed under reduced pressure. The residue was worked up with dichloromethane and dried over anhydrous sodium sulfate. The crude product obtained was purified by column chromatography (eluent: 20% ethyl acetate/light petroleum) to afford **13** as a white solid (0.596 g, 98%). R_f=0.33; m.p. 140–143°C; $[\alpha]_D^{25}=+25.6$ (c=1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ=8.13–8.22 (m, 2H; Ar H), 7.87–7.96 (m, 2H; Ar H), 7.43–7.65 (m, 4H; Ar H), 7.21–7.32 (m, 7H; Ar H), 5.80 (dt, 1H, J=3.9, 1.6 Hz; Ins H), 5.64–5.70 (m, 2H; Ins H, HCO_3), 4.70–4.75 (m, 1H; Ins H), 4.52–4.69 (m, 4H; CH_2, Ins H), 4.48 ppm (dt, 1H, J=3.8, 1.7 Hz); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): δ=166.1 (C=O), 165.3 (C=O), 136.7 (C_{arom}), 133.4 (C_{arom}), 133.3 (C_{arom}), 129.9 (C_{arom}), 129.5 (C_{arom}), 128.9 (C_{arom}), 128.43 (C_{arom}), 128.37 (C_{arom}), 128.0 (C_{arom}), 127.9 (C_{arom}), 103.2 (HCO_3), 73.4 (Ins C), 72.1 (CH_2), 69.9 (Ins C), 69.6 (Ins C), 68.1 (Ins C), 67.4 (Ins C), 64.2 ppm (Ins C); IR ($CHCl_3$): $\tilde{\nu}$=1724 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{24}O_8$: C 68.84, H 4.95; found: C 68.93, H 4.89.

D-6-*O*-Benzyl-*myo*-inositol (14): A mixture of the orthoformate **12** (0.07 g, 0.25 mmol), trifluoroacetic acid (0.8 mL) and water (0.1 mL) was stirred at room temperature for 24 h. The solvents were removed under reduced pressure and the residue was co-evaporated with dry toluene. The white solid obtained was crystallized from methanol/dichloromethane 1:4 at ≈0°C to give **14** as white needle-type crystals (0.059 g, 87%). m.p. 175–176°C (lit.:[29a] m.p. 176–178°C); $[\alpha]_D^{29}=6.4$ (c=1 in MeOH) (lit.:[29a] $[\alpha]_D^{22}=-6.4$ (c=1 in MeOH))).

D-2,4-Di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate (1): A solution of the benzyl ether **13** (0.489 g, 1.0 mmol) in methanol (3 mL) and ethyl acetate (3 mL) was hydrogenolyzed in the presence of 20% $Pd(OH)_2$/C

(0.040 g) at 50 psi. After 6 h, the reaction mixture was filtered over a short bed of Celite, which was subsequently washed with ethyl acetate (10 mL). Evaporation of the solvents from the filtrate and washings under reduced pressure followed by column chromatography (eluent: ethyl acetate/light petroleum 1:2) afforded **1** as a white solid (0.380 g, 95%). The dibenzoate **1** could be crystallized for single-crystal X-ray diffraction studies by slow diffusion of light petroleum into a chloroform solution of **1** in a closed container at RT. $R_f = 0.27$; m.p. 162–164°C; $[\alpha]_D^{22} = +66.0$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): $\delta = 8.02$–8.20 (m, 4H; Ar H), 7.55- 7.70 (m, 2H; Ar H), 7.39–7.54 (m, 4H; Ar H), 5.83 (dt, 1H, $J = 3.7$, 1.6 Hz; Ins H), 5.62–5.75 (m, 2H; Ins H, HCO_3), 4.70–4.82 (m, 1H; Ins H), 4.56–4.67 (m, 2H; Ins H), 4.45–4.55 (m, 1H; Ins H), 2.69 ppm (d, 1H, $J = 5.8$ Hz; OH); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): $\delta = 166.3$ (C=O), 165.3 (C=O), 133.6 (C_{arom}), 129.9 (C_{arom}), 129.8 (C_{arom}), 129.3 (C_{arom}), 128.8 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 102.9 (HCO_3), 71.7 (Ins C), 69.6 (Ins C), 68.5 (Ins C), 68.4 (Ins C), 67.2 (Ins C), 63.8 ppm (Ins C); IR ($CHCl_3$): $\tilde{\nu} = 3540$–3240, 1701, 1728 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{18}O_8$: C 63.31, H 4.55; found: C 63.21, H 4.29.

D-2,6-Di-*O*-tosyl-4-*O*-benzyl-*myo*-inositol-1,3,5-orthoformate (*ent*-11): D-2,6-Di-*O*-tosyl-*myo*-inositol-1,3,5-orthoformate (*ent*-**10**, 0.701 g, 1.41 mmol) was benzylated with benzyl bromide (0.25 mL, 2.1 mmol) in dry DMF (8 mL) and sodium hydride (0.068 g, 1.70 mmol) as in the preparation of **11** to give *ent*-**11** as a white solid (0.778 g, 94%). $R_f = 0.29$; m.p. 75–78°C; $[\alpha]_D^{25} = +8.8$ ($c = 1$ in chloroform); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): $\delta = 7.68$–7.83 (m, 4H; Ar H), 7.21–7.40 (m, 9H; Ar H), 5.43 (d, 1H, $J = 1.3$ Hz; HCO_3), 5.08 (dt, 1H, $J = 3.9$, 1.64 Hz; Ins H), 4.89–4.96 (m, 1H; Ins H), 4.42–4.65 (q, 2H, $J = 11.6$ Hz; CH_2), 4.35–4.41 (m, 1H; Ins H), 4.24 (dt, 1H, $J = 4.1$, 1.65 Hz; Ins H), 4.12–4.20 (m, 1H; Ins H), 4.01–4.10 (m, 1H; Ins H), 2.47 (s, 3H; CH_3), 2.43 ppm (s, 3H; CH_3); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): $\delta = 145.6$ (C_{arom}), 145.3 (C_{arom}), 136.7 (C_{arom}), 132.9 (C_{arom}), 132.3 (C_{arom}), 130.0 (C_{arom}), 129.9 (C_{arom}), 128.4 (C_{arom}), 127.9 (C_{arom}), 127.8 (C_{arom}), 127.4 (C_{arom}), 126.8 (C_{arom}), 102.5 (HCO_3), 72.3 (Ins C), 72.1 (Ins C), 71.3 (CH_2), 69.9 (Ins C), 69.6 (Ins C), 68.7 (Ins C), 67.1 (Ins C), 21.6 (CH_3), 21.5 ppm (CH_3); elemental analysis calcd (%) for $C_{28}H_{28}O_{10}S_2$: C 57.13, H 4.79, S 10.89; found: C 57.4, H 4.53, S 11.03.

D-4-*O*-Benzyl-*myo*-inositol-1,3,5-orthoformate (*ent*-12): Methanolysis of *ent*-**11** (0.589 g, 1.0 mmol) with sodium methoxide (0.541 g, 10.02 mmol) in dry methanol (8 mL) as in the preparation of **12** gave *ent*-**12** as a gum (0.275 g, 98%). $R_f = 0.28$; $[\alpha]_D^{27} = +15.3$ ($c = 1$ in ethanol); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): $\delta = 7.23$–7.50 (m, 5H; Ar H), 5.44 (d, 1H, $J = 1.3$ Hz; HCO_3), 4.67 (q, 2H, $J = 11.6$ Hz; CH_2), 4.38–4.55 (m, 2H; Ins H), 4.18–4.35 (m, 3H; Ins H), 4.09 (s, 1H; Ins H), 3.75 (d, 1H, $J = 10.2$ Hz; OH), 3.23 ppm (s, 1H; OH); ^{13}C NMR ($CDCl_3$, 75.48 MHz, TMS): $\delta = 135.8$ (C_{arom}), 128.9 (C_{arom}), 128.8 (C_{arom}), 128.0 (C_{arom}), 102.7 (HCO_3), 74.7 (Ins C), 74.2 (Ins C), 73.0 (CH_2), 72.2 (Ins C), 67.8 (Ins C), 67.3 (Ins C), 60.6 ppm (Ins C); IR (neat): $\tilde{\nu} = 3200$–3550 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{16}O_6$: C 59.99, H 5.75; found: C 60.11, H 5.70.

D-2,6-Di-*O*-benzoyl-4-*O*-benzyl-*myo*-inositol-1,3,5-orthoformate (*ent*-13): Compound *ent*-**12** (0.25 g, 0.89 mmol) was benzoylated with benzoyl chloride (0.75 g, 5.33 mmol), dry pyridine (4 mL) and DMAP (0.01 g) as in the preparation of **13** to give *ent*-**13** as a white solid (0.418 g, 96%). $R_f = 0.35$; m.p. 140–142°C; $[\alpha]_D^{27} = -25.02$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): $\delta = 8.13$–8.21 (m, 2H; Ar H), 7.87–7.97 (m, 2H; Ar H), 7.43- 7.68 (m, 4H; Ar H), 7.20–7.33 (m, 7H; Ar H), 5.80 (dt, $J = 4.0$, 1.8 Hz 1H; Ins H), 5.64–5.70 (m, 2H; Ins H, HCO_3), 4.69–4.76 (m, 1H; Ins H), 4.52–4.68 (m, 4H; Ins H), 4.48 ppm (dt, 1H, $J = 3.8$, 1.6; Ins H); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): $\delta = 166.1$ (C=O), 165.3 (C=O), 136.7 (C_{arom}), 133.4 (C_{arom}), 133.3 (C_{arom}), 129.9 (C_{arom}), 129.5 (C_{arom}), 128.9 (C_{arom}), 128.4 (C_{arom}), 128.3 (C_{arom}), 128.0 (C_{arom}), 127.9 (C_{arom}), 103.2 (HCO_3), 73.4 (Ins C), 72.1 (CH_2), 69.9 (Ins C), 69.6 (Ins C), 68.1 (Ins C), 67.4 (Ins C), 64.2 ppm (Ins C); IR ($CHCl_3$): $\tilde{\nu} = 1722$ cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{24}O_8$: C 68.84, H 4.95; found: C 68.57, H 4.61.

D-4-*O*-Benzyl-*myo*-inositol (*ent*-14): Compound *ent*-**12** (0.021 g, 0.08 mmol) was treated with trifluoroacetic acid and water (0.4+0.1 mL) at room temperature for 24 h (as in the preparation of **14**) to give *ent*-**14** as white needle-type crystals (0.017 g, 84%). M.p. 175–176°C (lit.:[29a] m.p. 175–177°C); $[\alpha]_D^{30} = +6.4$ ($c = 1$ in MeOH) (lit.:[29a] $[\alpha]_D^{22} = +6$ ($c = 1$ in MeOH)).

D-2,6-Di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate (*ent*-1): A solution of *ent*-**13** (0.3 g, 0.61 mmol) was hydrogenolyzed in methanol (2 mL) and ethyl acetate (3 mL) in the presence of 20% $Pd(OH)_2$/C (0.025 g) as in the preparation of **1** to give *ent*-**1** as a white solid (0.234 g, 96%). The dibenzoate *ent*-**1** could be crystallized for single-crystal X-ray diffraction studies by slow diffusion of light petroleum into a chloroform solution of *ent*-**1** in a closed container at RT. $R_f = 0.28$; m.p. 163–165°C; $[\alpha]_D^{27} = -65.1$ ($c = 1$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, TMS): $\delta = 8.10$–8.20 (m, 2H; Ar H), 7.99–8.09 (m, 2H; Ar H), 7.54–7.66 (m, 2H; Ar H), 7.40–7.52 (m, 4H; Ar H), 5.84 (dt, 1H, $J = 4.0$, 1.8 Hz; Ins H), 5.63–5.70 (m, 2H; Ins H, HCO_3), 4.69–4.81 (m, 1H; Ins H), 4.56–4.67 (m, 2H; Ins H), 4.45–4.54 (m, 1H; Ins H), 2.65 ppm (d, 1H, $J = 5.4$ Hz; OH); ^{13}C NMR ($CDCl_3$, 50.3 MHz, TMS): $\delta = 166.3$ (C=O), 165.3 (C=O), 133.7 (C_{arom}), 133.5 (C_{arom}), 129.9 (C_{arom}), 129.8 (C_{arom}), 129.3 (C_{arom}), 128.8 (C_{arom}), 128.6 (C_{arom}), 128.5 (C_{arom}), 102.9 (HCO_3), 71.7 (Ins C), 69.6 (Ins C), 68.5 (Ins C), 68.4 (Ins C), 67.3 (Ins C), 63.8 ppm (Ins C); IR ($CHCl_3$): $\tilde{\nu} = 3412$, 1722, 1703 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{18}O_8$: C 63.31, H 4.55; found: C 63.01, H 4.41.

Crystallization of *rac*-2,4-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoacetate (*rac*-3) in the presence of D-2,6-di-*O*-benzoyl-*myo*-inositol-1,3,5-orthoformate (*ent*-1): The orthoacetate *rac*-**3** (0.052 g, 0.13 mmol) and the orthoformate *ent*-**1** (0.005 g, 0.01 mmol) were dissolved in chloroform (3 mL). Light petroleum was diffused into this solution in a closed container over 4–5 days at RT. Clusters of sharp needles (0.044 g) were obtained. The sharp needles were separated and collected (0.037 g). Use of a larger amount of *ent*-**1** (0.010 g or 0.050 g) for the crystallization experiment (as above) did not make any difference in the yield of form II crystals. However, the use of a lesser amount of *ent*-**1** (0.002 g) for the crystallization experiment (as above) resulted in concomitant formation of both form I and II crystals of *rac*-**3**. Form I crystals appeared faster than the form II crystals. Crystallization of *rac*-**3** in the absence of *ent*-**1** in chloroform resulted in form I crystals (2–3 days) alone. Similar results were obtained on crystallization of the racemic orthoacetate *rac*-**3** in the presence of **1**.

Note: The ^{1}H NMR spectrum of the clusters of from II crystals showed that they contained *rac*-**3** and *ent*-**1** in the ratio 11:1. The ratio of the two dibenzoates in manually separated needles (from clusters) was 20:1. The variation in the relative amount of the two dibenzoates present in form II crystals suggested that the form II crystals are a polymorphic modification of the racemic orthoacetate (*rac*-**3**) contaminated with the enatiomeric orthoformate rather than co-crystals of the two dibenzoates. This was confirmed by single-crystal X-ray diffraction data of form II crystals and the thermal transformation of form II crystals to form I crystals. Washing of the crystals of *rac*-**3** to free them from the adhering *ent*-**1** is not practical because both the dibenzoates have a similar solubility in organic solvents.

Thermal analysis: The thermal behaviour of dimorphs of *rac*-**3** was investigated by measuring the enthalpy change on a Mettller differential scanning calorimeter instrument. About 3–5 mg of crystals were placed on an aluminium pan (5 mm diameter) and were analysed from room temperature to 200°C by using an empty pan as the reference. The heating rate was 10°C min^{-1} and nitrogen gas was used for purging. DSC analysis (Figure 3) of form II crystals of *rac*-**3** indicated a phase change around 145–150°C. Analysis of the crystals by X-ray diffraction revealed that this polymorph underwent crystal-to-crystal transformation on heating at 145°C to give form I crystals.

Solid-state transesterification reaction of form II crystals of *rac*-3: Form II crystals of *rac*-**3** (0.032 g, 0.08 mmol) and anhydrous sodium carbonate (0.07 g, 0.7 mmol) were mixed together and ground to a fine powder by using a pestle and mortar. This mixture was heated in a glass stoppered test tube at 115°C under an argon atmosphere for 195 h. The reaction mixture was cooled to room temperature and the products were extracted with chloroform/methanol 1:1 (2×10 mL). The mixture of products obtained on evaporation of the solvent was separated by preparative TLC to give the tribenzoate **6** (0.017 g, 42%; m.p. 153–155°C (lit.:[36] m.p. 154–155°C)) and the diol **9** (0.01 g, 42%; m.p. 158–159°C (lit.:[37] m.p. 160°C)) as white solids.

Note: We have observed earlier that the crystal structure of dibenzoates analogous to *rac*-**3** remains unaffected on grinding with sodium carbonate. For details see reference [21].

Solid-state transesterification reaction of form I crystals of *rac*-3: The reaction was carried out as above by using form I crystals of the orthoacetate *rac*-**3** (0.103 g, 0.25 mmol) and anhydrous sodium carbonate (0.212 g, 2.0 mmol) at 115 °C for 195 h. The tribenzoate **6** (0.017 g, 13 %) and the starting material *rac*-**3** (0.024 g, 23 %) were separated from the mixture of products formed[21b] by column chromatography using a mixture of ethyl acetate/dichloromethane/petroleum ether 1:1:8 as the eluent.

X-ray crystallography: Single-crystal X-ray structures were determined for form II crystals of *rac*-**3** and the enatiomeric orthoformate *ent*-**1**. All the crystals were stable at room temperature and the intensity data measurements were carried out at room temperature (297 K) on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized ($Mo_{K\alpha}$ = 0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. Data were collected with a ω scan width of 0.3° at four different settings of ϕ (0, 90, 180 and 270°) keeping the sample-to-detector distance fixed at 6.145 cm and the detector position (2θ) fixed at −28°. X-ray data collection was monitored by the SMART program (Bruker, 2003). All the data were corrected for Lorentzian, polarization and absorption effects by using SAINT and SADABS programs (Bruker, 2003). SHELX-97 was used for structure solution and full-matrix least-squares refinement on F^2. Hydrogen atoms for the enantiomer *ent*-**1** were located from a difference Fourier map, and their positional coordinates and isotropic thermal parameters were refined. H atoms in form II crystals of *rac*-**3** were included in the refinement as per the riding model. Molecular and packing diagrams were generated by using ORTEP-32 and Mercury-1.5. Geometrical calculations were performed by using SHELXTL (Bruker, 2003) and PLATON. Table 4 summarizes the crystallographic data for form II crystals of *rac*-**3** and *ent*-**1**.

Table 4. Summary of crystal data, data collection, structure solution and refinement details for form II crystals of *rac*-**3** and *ent*-**1**.

Crystal data	*rac*-**3** (form II)	*ent*-**1**
formula	$C_{22}H_{20}O_8$	$C_{21}H_{18}O_8$
M_r	412.38	398.35
crystal size [mm]	0.78×0.10×0.08	0.69×0.19×0.12
T [K]	297(2)	297(2)
crystal system	monoclinic	orthorhombic
space group	$C2/c$	$P2_12_12_1$
a [Å]	27.591(7)	5.914(2)
b [Å]	9.383(3)	16.229(6)
c [Å]	16.938(4)	18.957(7)
β [°]	117.346(4)	90
V [Å^3]	3895.0(18)	1819.3(12)
Z	8	4
$F(000)$	1728	832
ρ calcd [g cm^{-3}]	1.406	1.454
μ [mm^{-1}]	0.108	0.113
absorption correction	multiscan	multiscan
T_{min}	0.9205	0.9265
T_{max}	0.9912	0.9862
reflns. collected	13715	11640
unique reflns.	3422	3200
observed reflns.	2857	2956
index range	$-32 \le h \le 32$, $-11 \le k \le 11$, $-20 \le l \le 19$	$-6 \le h \le 7$, $-19 \le k \le 19$, $-22 \le l \le 22$
R_1 [$I > 2\sigma(I)$]	0.0693	0.0344
wR_2	0.1468	0.0779
R_1 (all data)	0.0834	0.0379
wR_2 (all data)	0.1534	0.0797
goodness-of-fit	1.214	1.099
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [eÅ^{-3}]	0.178, −0.259	0.127, −0.119

CCDC-690376 (*rac*-**3**) and -690375 (*ent*-**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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[1] a) M. A. Garcia-Garibay, *Curr. Opin. Solid State Mater. Sci.* **1998**, *3*, 399–406; b) M. A. Garcia-Garibay, A. E. Constable, J. Jernelius, T. Choi, D. Cizmeciyan, S. H. Shin, *Physical Supramolecular Chemistry*, Kluwer Academic Publishers, Dordrecht, **1996**.

[2] a) M. D. Cohen, G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 1996–2000; b) M. D. Cohen, G. M. J. Schmidt, F. I. Sonntag, *J. Chem. Soc.* **1964**, 2000–2014; c) G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 2014–2021; d) K. Honda, F. Nakanishi, N. Feeder, *J. Am. Chem. Soc.* **1999**, *121*, 8246–8250; e) T. Obata, T. Shimo, M. Yasutake, T. Shinmyozu, M. Kawaminami, R. Yoshida, K. Somekawa, *Tetrahedron* **2001**, *57*, 1531–1541; f) S. Nagahama, K. Inoue, K. Sada, M. Miyata, A. Matsumoto, *Cryst. Growth Des.* **2003**, *3*, 247–256; g) X. Gao, T. Friščić, L. R. MacGillivray *Angew. Chem.* **2004**, *116*, 234–238; *Angew. Chem. Int. Ed.* **2004**, *43*, 232–236; h) K. Takaoka, M. Kawano, T. Ozekib, M. Fujita, *Chem. Commun.* **2006**, 1625–1627.

[3] a) A. O. Patil, D. Y. Curtin, I. C. Paul, *J. Am. Chem. Soc.* **1984**, *106*, 348–353; b) A. O. Patil, D. Y. Curtin, I. C. Paul, *J. Am. Chem. Soc.* **1984**, *106*, 4010–4015; c) J. R. Scheffer, Y. F. Wong, A. O. Patil, D. Y. Curtin, I. C. Paul, *J. Am. Chem. Soc.* **1985**, *107*, 4898–4904; d) A. O. Patil, W. T. Pennington, G. R. Desiraju, D. Y. Curtin, I. C. Paul, *Mol. Cryst. Liq. Cryst.* **1986**, *134*, 279–304; e) K. Vyas, H. Manohar, K. Venkatesan, *J. Phys. Chem.* **1990**, *94*, 6069–6073; f) M. Kaftory in *Organic Solid State Reaction* (Ed.: F. Toda), Kluwer Academic Publishers, Dordrecht, **2002**, pp. 47–67; g) D. Braga, F. Grepioni, *Angew. Chem.* **2004**, *116*, 4092–4102; *Angew. Chem. Int. Ed.* **2004**, *43*, 4002–4011.

[4] H. E. Zimmerman, I. V. Alabugin, W. Chen, Z. Zhu, *J. Am. Chem. Soc.* **1999**, *121*, 11930–11931.

[5] a) J. N. Gamlin, R. Jones, M. Leibovitch, B. Patrick, J. R. Scheffer, J. Trotter, *Acc. Chem. Res.* **1996**, *29*, 203–209; b) J. R. Scheffer, W. J. Xia, *Top. Curr. Chem.* **2005**, *254*, 233–262; c) E. Y. Cheung, K. D. M. Harris, T. Kang, J. R. Scheffer, J. Trotter, *J. Am. Chem. Soc.* **2006**, *128*, 15554–15555.

[6] a) F. Toda, *Acc. Chem. Res.* **1995**, *28*, 480–486; b) A. E. Keating, M. A. Garcia-Garibay in *Molecular and Supramolecular Photochemistry, Vol. 2* (Eds.: V. Ramamurthy, K. Schanze), Marcel Dekker, New York, **1998**, pp. 195–248; c) L. R. MacGillivray, *NATO Science Series II: Mathematics, Physics and Chemistry, Vol. 68*, Springer, Berlin, **2002**, pp. 355–365; d) C. J. Mortko, M. A. Garcia-Garibay, *J. Am. Chem. Soc.* **2005**, *127*, 7994–7995.

[7] a) J. O. Metzger, *Angew. Chem.* **1998**, *110*, 3145–3148; *Angew. Chem. Int. Ed.* **1998**, *37*, 2975–2978; b) J. H. Kim, S. M. Hubig, S. V. Lindeman, J. K. Kochi, *J. Am. Chem. Soc.* **2001**, *123*, 87–95.

[8] H. Koshima, H. Kawanishi, M. Nagano, H. Yu, M. Shiro, T. Hosoya, H. Uekusa, Y. Ohashi, *J. Org. Chem.* **2005**, *70*, 4490–4497.

[9] a) D. G. Amirsakis, M. A. Garcia-Garibay, S. J. Rowan, J. F. Stoddart, A. J. P. White, D. J. Williams, *Angew. Chem.* **2001**, *113*, 4386–4391; *Angew. Chem. Int. Ed.* **2001**, *40*, 4256–4261; b) B. Hatano, S.-y. Hirano, T. Yanagihara, S. Toyota, F. Toda, *Synthesis* **2001**, 1181–1184; c) S. Nakamatsu, K. Yoshizawa, S. Toyota, F. Toda, I. Matijasic, *Org. Biomol. Chem.* **2003**, *1*, 2231–2234; d) C. B. Aakeröy, J. Desper, B. M. T. Scott, *Chem. Commun.* **2006**, 1445–1447.

[10] a) V. Ramamurthy, K. Venkatesan, *Chem. Rev.* **1987**, *87*, 433–481; b) L. R. MacGillivray, J. L. Reid, J. A. Ripmeester, *J. Am. Chem. Soc.* **2000**, *122*, 7817–7818; c) M. A. Garcia-Garibay, *Acc. Chem. Res.* **2003**, *36*, 491–498; d) T. Caronna, R. Liantonio, T. A. Logothetis, P. Metrangolo, T. Pilati, G. Resnati, *J. Am. Chem. Soc.* **2004**, *126*, 4500–4501.
[11] T. Friščić′, L. Fábián, J. C. Burley, W Jones, W. D. S. Motherwell, *Chem. Commun.* **2006**, 5009–5011.
[12] a) F. Toda, *Synlett* **1993**, 303–312; b) F. Toda, *Aust. J. Chem.* **2001**, *54*, 573–582; c) R. Sakurai, S. Suzuki, J. Hashimoto, M. Baba, O. Itoh, A. Uchida, T. Hattori, S. Miyano, M. Yamaura, *Org. Lett.* **2004**, *6*, 2241–2244.
[13] H. Vancik, V. Simunic-Meznaric, E. Mestrovic, I. Halasz, *J. Org. Chem.* **2004**, *69*, 4829–4834.
[14] L. M. Campos, H. Dang, D. Ng, Z. Yang, H. L. Martinez, M. A. Garcia-Garibay, *J. Org. Chem.* **2002**, *67*, 3749–3754.
[15] a) J. D. Dunitz, *Chem. Commun.* **2003**, 545–548; b) J. D. Dunitz, A. Gavezzotti, *Angew. Chem.* **2005**, *117*, 1796–1819; *Angew. Chem. Int. Ed.* 2005, 44, 1766–1787.
[16] a) L. Yu, *J. Am. Chem. Soc.* **2003**, *125*, 6380–6381; b) C. Desgranges, J. Delhommelle, *J. Am. Chem. Soc.* **2006**, *128*, 15104–15105.
[17] a) R. J. Davey, N. Blagden, G. D. Potts, R. Docherty, *J. Am. Chem. Soc.* **1997**, *119*, 1767–1772; b) C.-H. Gu, K. Chatterjee, V. Young, Jr., D. J. W. Grant, *J. of Crystal Growth* **2002**, *235*, 471–481.
[18] A. Gavezzotti, *Synlett* **2002**, 0201–0214.
[19] J. D. Watson, F. H. Crick, *Ann. N. Y. Acad. Sci.* **1995**, *758*, 194.
[20] a) P. K. Thallapally, R. K. R. Jetti, A. K. Katz, H. L. Carrell, K. Singh, K. Lahiri, S. Kotha, R. Boese, G. R. Desiraju, *Angew. Chem.* **2004**, *116*, 1169–1175; *Angew. Chem. Int. Ed.* **2004**, *43*, 1149–1155; b) K. Sangwal, *Additives and Crystallization Processes: From Fundamentals to Applications*, Wiley, New York, **2007**, p. 319.
[21] a) T. Praveen, U. Samanta, T. Das, M. S. Shashidhar, P. Charkrabarti, *J. Am. Chem. Soc.* **1998**, *120*, 3842–3845; b) M. P. Sarmah, R. G. Gonnade, M. S. Shashidhar, M. M. Bhadbhade, *Chem. Eur. J.* **2005**, *11*, 2103–2110; c) C. Murali, M. S. Shashidhar, R. G. Gonnade, M. M. Bhadbhade, *Eur. J. Org. Chem.* **2007**, 1153–1159.
[22] a) J. A. Brannigan, G. Dodson, H. J. Duggleby, P. C. E. Moody, J. L. Smith, D. R. Tomchick, A. G. Murzin, *Nature* **1995**, *378*, 416–419; b) D. Voet, J. G Voet, *Mechanisms of Enzyme Action and Metabolism, Biochemistry, Vol. 1*, Wiley, New York, **2003**.
[23] a) H. B. Bürgi, J. D. Dunitz, E. Shefter, *J. Am. Chem. Soc.* **1973**, *95*, 5065–5067; b) H. B. Bürgi, J. D. Dunitz, E. Shefter, *Acta Crystallogr. Sect. B* **1974**, *30*, 1517–1527; c) H. B. Bürgi, J.-M. Lehn, G. J. Wipff, *J. Am. Chem. Soc.* **1974**, *96*, 1956–1957; d) H. B. Bürgi, J. D. Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153–161.
[24] a) M. Nishio, M. Hirota, Y. Umezawa, *The CH/π Interaction: Evidence, Nature and Consequences*, Wiley-VCH, Weinheim, **1998**; b) S. Re, S. Nagase, *Chem. Commun.* **2004**, 658–659; c) K. Watanabe, T. Uno, T. Koshiba, T. Okamoto, Y. Ebara, S-i. Ueji, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 543–548; d) M. Nishio, *Tetrahedron* **2005**, *61*, 6923–6950; e) M. Harigai, M. Kataoka, Y. Imamoto, *J. Am. Chem. Soc.* **2006**, *128*, 10646–10647.
[25] J. Huang, S. Chen, I. A. Guzei, L. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 11985–11992.
[26] I. Solomonov, M. Osipova, Y. Feldman, C. Baehtz, K. Kjaer, I. K. Robinson, G. T. Webster, D. McNaughton, B. R. Wood, I. Weissbuch, L. Leiserowitz, *J. Am. Chem. Soc.* **2007**, *129*, 2615–2627.
[27] I. Weissbuch, M. Lahav, L. Leiserowitz, *Cryst. Growth Des.* **2003**, *3*, 125–150, and references therein.
[28] M. P. Sarmah, M. S. Shashidhar, K. M. Sureshan, R. G. Gonnade, M. M. Bhadbhade, *Tetrahedron* **2005**, *61*, 4437–4446.
[29] a) P. J. Garegg, B. Lindberg, *Carbohydr. Res.* **1985**, *139*, 209–215; b) J. P. Vacca, S. J. deSolms, J. R. Huff, *J. Am. Chem. Soc.* **1987**, *109*, 3478–3479; c) S. Ozaki, Y. Kondo, H. Nakahira, S. Yamaoka, Y. Watanabe, *Tetrahedron Lett.* **1987**, *28*, 4691–4694; d) G. Baudin, B. I. Glänzer, K. S. Swaminathan, A. Vasella, *Helv. Chim. Acta* **1988**, *71*, 1367–1378; e) D.-M. Gou, Y.-C. Liu, C-S. Chen, *Carbohydr. Res.* **1992**, *234*, 51–63; f) M. T. Rudolf, T. Kaiser, A. H. Guse, G. W. Mayr, C. Schultz, *Liebigs Ann.* **1997**, *1997*, 1861–1869; g) L. W. Leung, R. Bittman, *Carbohydr. Res.* **1997**, *305*, 171–179.
[30] M. A. L. Podeschwa, O. Plettenburg, H. J. Altenbach, *Eur. J. Org. Chem.* **2005**, 3116–3127, and references therein.
[31] R. Daniellou, H. Heng, D. M. Langill, D. A. R. Sanders, D. R. J. Palmer, *Biochemistry* **2007**, *46*, 7469–7477.
[32] K. M. Sureshan, T. Das, M. S. Shashidhar, R. G. Gonnade, M. M. Bhadbhade, *Eur. J. Org. Chem.* **2003**, 1035–1041.
[33] K. Sawada, D. Hashizume, A. Sekina, H. Uekusa, K. Kato, Y. Ohashi, K. Kakinuma, Y. Ohgo, *Acta. Cryst.* **1996**, *B52*, 303–313.
[34] *Purification of Laboratory Chemicals*, 2nd ed., D. D. Perrin, W. L. F. Armarego, Pergamon Press, Oxford, **1988**.
[35] G. Baudin, B. I. Glänzer, K. S. Swaminathan, A. Vasella, *Helv. Chim. Acta* **1988**, *71*, 1367–1378.
[36] T. Praveen, M. S. Shashidhar, *Carbohydr. Res.* **2001**, *330*, 409–411.
[37] a) K. M. Sureshan, Ph.D thesis, University of Pune (India), **2002**, p. 89; b) K. M. Sureshan, M. S. Shashidhar, *Tetrahedron Lett.* **2000**, *41*, 4185–4188.

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