Efficient resolution of *rac*-2,3-*O*-isopropylideneglycerol by enantioselective inclusion crystallization with the chiral diol CYTOL

Maxim G. Vinogradov,*[a] Dmitry V. Kurilov,[a] Vladimir A. Ferapontov[a] and Glenn L. Heise[b]

[a] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation. Fax: +7 095 135 5328; e-mail: ving@ioc.ac.ru*

[b] *Cambrex Corporation, One Meadowlands Plaza, East Rutherford, NJ 07073, USA*

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The efficient resolution of *rac*-2,3-*O*-isopropylideneglycerol (IPG) using enantioselective two-step inclusion crystallization with the chiral diol CYTOL has been performed.

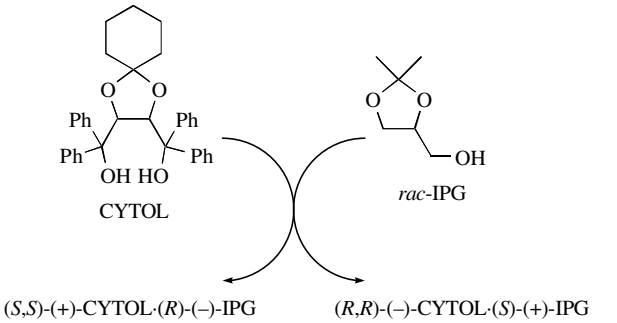
The chiral C_3 synthons (*R*)- and (*S*)-2,3-*O*-isopropylideneglycerols (IPG)[1] are used for the syntheses of various biologically active compounds such as lipids,[2–4] antibiotics[5] and β-blockers.[6,7] Optically active IPG is often obtained from natural sources: D-mannitol,[8] L-ascorbic acid[9] and L-serine[10] or by the resolution of racemic IPG. IPG enantiomers are resolved using either a classic approach (*via* diastereomeric salts) or enzymatic methods. However, in the former case, the chemical modification of IPG (for example, by phthalic anhydride[11(*a*)] or its analogues[11(*b*)]) is required, whereas in the latter case enantioselectivity of the IPG resolution is insufficiently high for preparative goals (as a rule, no more than 65% *ee*).[12–14]

The resolution of *rac*-IPG by inclusion crystallization was reported.[15] Using chiral 2,3-*O*-cyclohexylidene-1,1,4,4-tetraphenylthreitol (CYTOL) as a host compound and toluene–hexane as a solvent, (*S*)-(+)-IPG was obtained in 38% yield.

In this work, based on a latter approach, an efficient two-stage resolution of *rac*-IPG has been performed by applying, at the first stage, inclusion crystallization in a suspension of a resolving agent. For the resolution, a suspension of (*R*,*R*)- or (*S*,*S*)-CYTOL in hexane was used.†

We found that the efficiency of the IPG inclusion crystallization rises with increasing the IPG/CYTOL molar ratio in the starting mixture, reaching 85–86% *ee* at the ratio IPG/CYTOL = 4 (Table 1, entries 1–4), the enantioselectivity remaining the same with a further increase of this ratio up to 10. To achieve higher optical purity of IPG included into IC, two approaches are, in principle, possible: the recrystallization of IC or the binding of the minor enantiomer of IPG into IC with CYTOL of the opposite configuration.

To select the preferable variant of further enrichment of chiral IPG (Stage 2), the inclusion crystallization of IPG containing 80% (*S*)-enantiomer was carried out using both (*R*,*R*)- and (*S*,*S*)-CYTOL as resolving agents (Table 1, entries 5 and 6). To our surprise, in both cases, enrichment by the (*S*)-enantiomer of IPG took place regardless of CYTOL configuration, both crystalline ICs being of identical stoichiometric composition (CYTOL/IPG = 1:1). To our knowledge, it is the first example of inclusion complexation when both enantiomers of the resolving agent are capable of giving IC enriched in the same enantiomer of the substrate. At the same time, for the combination of (*S*)-(+)-IPG–(*R*,*R*)-(–)-CYTOL, the yield of IC and enantiomeric enrichment degree of the applied substrate is higher than that for the combination (*S*)-(+)-IPG–(*S*,*S*)-(+)-CYTOL (Table 1, entries 5 and 6). This result could be foreseen because in the case of the resolution of *rac*-IPG (*R*,*R*)-(–)-CYTOL gives IC preferably with (*S*)-IPG and, on the contrary, (*S*,*S*)-(+)-CYTOL forms IC selectively with (*R*)-IPG. This preference is stable as two series of 10 repeated experiments each performed with (*S*,*S*)- and (*R*,*R*)-CYTOL (Table 1, entries 3 and 4, respectively) gave the same stereochemical results in each series.



Scheme 1

The ability of (*R*,*R*)- and (*S*,*S*)-CYTOL to give IC containing the same prevailing enantiomer of IPG allows one to explain the dependence of the IPG resolution stereoselectivity on the starting molar ratio IPG/CYTOL (Table 1). In the case when the *rac*-IPG/CYTOL ratio is 2:1 [or 1:1 with respect to the (*R*)-enantiomer of *rac*-IPG], a considerable excess of (*S*)-IPG is formed while crystallization of the (*R*)-containing IC proceeds. Due to that, probability of crystallization of the unwanted (*S*)-containing IC increases (*cf.* entry 6) thus decreasing the inclusion complexation stereoselectivity. At the same time, a four-fold or higher excess of *rac*-IPG in the starting mixture prevents considerable change of the IPG enantiomeric composition compared with *rac*-IPG in the course of stereoselective inclusion crystallization.

As it follows from data presented in Table 2, the (*S*,*S*)-CYTOL·(*R*)-IPG complex remains unchanged after heating *in vacuo* at 50 °C for 0.5 h, whereas its heating at 80 °C results in loss of the IPG completely for the same period of time. In the latter case, the crystalline residue was found to be pure (*S*,*S*)-CYTOL, which can be used again for the resolution of *rac*-IPG.

Based on the above results (Tables 1 and 2), the preparative

† *Resolution procedure for* rac-*IPG*. *rac*-IPG (10 mmol, 1.32 g) was added to a suspension of (*S*,*S*)-(+)-CYTOL (2.5 mmol, 1.27 g) in hexane (50 ml), and the mixture was stirred for 24 h at room temperature. The obtained IC was filtered off, washed with cold hexane (5 ml) and dried at room temperature *in vacuo* (1–2 Torr). 1.33 g of IC was isolated. Then, it was recrystallised from diethyl ether (15 ml)–hexane (75 ml) at –18 °C for 24 h to give 0.94 g (71%) of the inclusion complex. It was dried *in vacuo* at room temperature. To liberate IPG from IC, the latter was heated at 80–90 °C *in vacuo* condensing the liberated IPG in a trap cooled by dry ice. 0.198 g (60% with respect to the starting reagents) of (*R*)-IPG (97% *ee*, GLC) has been isolated. $[\alpha]_D$ –11.05 (*c* 1, MeOH). Crystalline residues obtained after thermodissociation of IC and after evaporation of the mother liquid (after the recrystallization of IC) were united and dried *in vacuo* at 100 °C for 1 h. 1.16 g (92%) of pure (*S*,*S*)-(+)-CYTOL was isolated.

Enantiomeric composition of IPG was dermined for its acetate obtained by acetylation of the alcohol with Ac_2O in CH_2Cl_2 in the presence of pyridine. Analysis was carried out by GLC on a Biokhrom-21 instrument using a 30 m × 0.25 mm × 0.25 μm quartz capillary column (Supelco). The carrier gas (He) pressure before the column was 10 atm; the gas flow rate was 1 ml min^{-1}, the column temperature was 105 °C; the detector and evaporator temperatures were 170 °C; the nonretainable gas used was CH_4. The retention times of the compounds were the following (min): CH_4, 1.8; (*R*)-(–)-IPG acetate, 14.7; (*S*)-(+)-IPG acetate, 15.4.

Table 1 Dependence of IC yield and enantiomeric purity of IPG liberated from IC on inclusion crystallization conditions.

Entry	IPG, starting ratio (*R*)/(*S*)	Resolving agent	Molar ratio CYTOL/IPG in starting solution	Solvent (v/v)	Procedure[a]	IC yield (%)	*ee* (%) for IPG obtained from IC
1	50:50	(*S*,*S*)-(+)-CYTOL	1:2	Hexane	A	70	56 (*R*)
2	50:50	(*S*,*S*)-(+)-CYTOL	1:3	Hexane	A	78	83 (*R*)
3	50:50	(*S*,*S*)-(+)-CYTOL	1:4	Hexane	A	83	85 (*R*)
4	50:50	(*R*,*R*)-(–)-CYTOL	1:4	Hexane	A	82	86 (*S*)
5	10:90	(*R*,*R*)-(–)-CYTOL	1:1	Ether–hexane (1:5)	B	73	97 (*S*)
6	10:90	(*S*,*S*)-(+)-CYTOL	1:1	Ether–hexane (1:5)	B	36	86 (*S*)

[a] A. *Rac*-IPG was added to a suspension of CYTOL (0.25 mmol) in hexane (5 ml) and the mixture was stirred at room temperature for 24 h. Then, IC thus obtained was filtered off, washed with cold hexane (2 ml) and dried *in vacuo* at 80–90 °C, distilling off IPG that is liberated from IC.
B. Crystallization was carried out from a solution of CYTOL (0.25 mmol) and IPG (0.25 mmol) in the indicated solvent (6 ml) at –18 °C for 24 h. IC was filtered off and treated as indicated above (A).

Table 2 Temperature dependence of thermodissociation degree of the complex (*S*,*S*)-(+)-CYTOL·(*R*)-(–)-IPG.[a]

T/°C	Molar ratio CYTOL/IPG
50	1:1
60	1:0.95
70	1:0.46
80	1:0

[a]IC composition after heating at corresponding temperature for 1 h *in vacuo* (1–2 Torr).

resolution of *rac*-IPG has been realised (see the procedure†) to give optically active IPG in 60% yield with an enantiomeric purity of 97% *ee*.

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