Lipase–triethylamine-mediated dynamic transesterification of a tricyclic acyloin having a latent *meso*-structure: a new route to optically pure oxodicyclopentadiene

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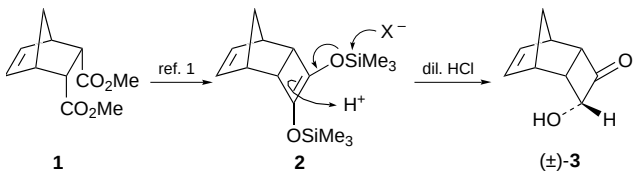
The racemic tricyclic acyloin (±)-*endo*-3-hydroxytricyclo[4.2.1.0^{2,5}]non-7-en-4-one has been dynamically resolved *via* the transient formation of the *meso*-enediol isomer under lipase–triethylamine-mediated kinetic transesterification conditions to give the single chiral acetate (−)-*endo*-3-acetoxytricyclo[4.2.1.0^{2,5}]non-7-en-4-one, serving as a precursor of (−)-oxodicyclopentadiene, in excellent optical and chemical yields.

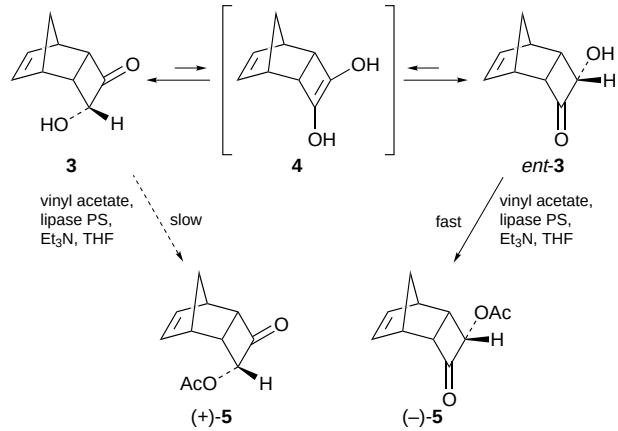
During the preparation of the racemic tricyclic acyloin 3-hydroxytricyclo[4.2.1.0^{2,5}]non-7-en-4-one (±)-**3** starting from *endo*-2,3-bis(methoxycarbonyl)bicyclo[2.2.1]hept-5-ene **1** by employing the acyloin condensation,[1] we observed[2] that an acid hydrolysis of the bis-trimethylsilyloxy intermediate **2** furnished stereoselectively the single racemic acyloin (±)-**3** having an *endo*-hydroxy group (Scheme 1).† The *endo*-hydroxy configuration of **3** did not change even in the presence of triethylamine, which brought about complete deuterium exchange of the methine hydrogen on the acyloin functionality with deuterium oxide within 10 h. This seemed to be due to facile equilibration between the acyloin **3** and the transient *meso*-1,2-enediol intermediate **4** followed by convex-face selective protonation of the latter under weak basic conditions. Since the analogues of **3** having cyclopentenol and cyclohexenol rings in place of the four-membered ring have been found to be kinetically better discriminated than those having an *exo*-hydroxy group under lipase-mediated transesterification conditions,[3] we assumed that dynamic kinetic resolution[4,5] should take place in a facile manner to give a single enantiomeric *endo*-acetate **5**. The racemic acyloin (±)-**3** might be subjected to the transesterification conditions in the presence of an appropriate lipase under favourable equilibrium conditions,[6] thus generating the transient enediol **4** having *meso* symmetry. We report herein the first example of the lipase-mediated dynamic transesterification of the racemic acyloin **3** leading to the highly optically enriched single *endo*-acetate (−)-**5** *via* the transient generation of the *meso*-enediol **4** in reaction with vinyl acetate in THF containing a catalytic amount of triethylamine (Scheme 2).

When the racemic acyloin **3** was stirred with vinyl acetate (1.2 equiv.) in THF containing triethylamine[3b,5a,7] (0.1 equiv.) in the presence of lipase PS‡ (*Pseudomonas* sp. immobilized on Celite, Amano) for 48 h at room temperature, transesterification occurred to give the optically active *endo*-acetate (−)-**5**, $[\alpha]_D^{24}$ −120.7 (*c* 2.0, $CHCl_3$), in 75% yield accompanied by a minor amount of 5-hydroxy-4-oxatricyclo[5.2.1.0^{2,6}]dec-8-en-3-one§ (10%) which was separated by silica gel column chromatography. The optical yield of the product was determined to be 97% ee by HPLC (chiral column CHIRALCEL OD, 5% Pr^{i}OH–hexane) indicating clearly that the dynamic kinetic resolution took place as expected. When the reaction was carried out without triethylamine, simple kinetic resolution occurred to give the same *endo*-acetate (−)-**5**, $[\alpha]_D^{26}$ −120.3 (*c* 1.0, $CHCl_3$), (> 99% ee, CHIRALCEL OD, 5% Pr^{i}OH–hexane) in 45% yield leaving 53% of the optically enriched starting acyloin (+)-**3**, $[\alpha]_D^{27}$ + 190.5 (*c* 0.9, $CHCl_3$) (92% ee, CHIRALCEL OD, 5% Pr^{i}OH–hexane); thus, this result indicates that the amine accelerated the equilibrium between **3** and *ent*-**3** *via* the *meso*-1,2-enediol **4**. When the racemic acyloin (±)-**3** was stirred with vinyl acetate in the same THF–triethylamine medium without the lipase, the transesterification which competes with the enzymatic reaction, although it occurred, proceeded very slowly to give the racemic *endo*-acetate (±)-**5** in less than 3% yield, leaving most of the starting material untouched after 48 h at room temperature. Taking these observations into account, we concluded that triethylamine is requisite for the present dynamic transesterification and the actual enantioselectivity exerted by the enzyme was higher than that observed.

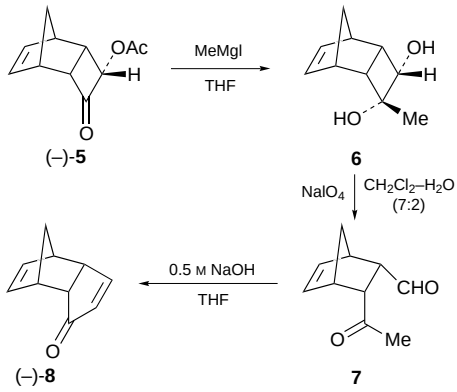
Having established the efficient dynamic kinetic transesterification of the racemic acyloin (±)-**3** having a latent *meso*-structure, the optically active acetate (−)-**5** thus obtained was next transformed into optically active oxodicyclopentadiene **8** so as to determine the absolute configuration of the resolved product as well as to probe its synthetic utility. Thus (−)-**5** was treated with excess MeMgI in THF to give the diol **6**, $[\alpha]_D^{26}$ −15.7 (*c* 0.6, $CHCl_3$), in nearly quantitative yield. Treatment of the diol **6** with sodium periodate gave the keto aldehyde **7** which was immediately exposed to diluted aqueous sodium hydroxide[8] to give the known oxodicyclopentadiene (−)-**8**, mp 74 °C, $[\alpha]_D^{26}$ −154.0 (*c* 1.0, $CHCl_3$) [lit.,[3b] mp 76 °C, $[\alpha]_D^{29}$ −158.5 (*c* 1.0, $CHCl_3$)] (> 99% ee by HPLC: CHIRALCEL OB, 10% Pr^{i}OH–hexane), in 50% overall yield by intramolecular aldolization.[8] Since optically active oxodicyclopentadiene **8** is



Scheme 1



Scheme 2



Scheme 3

interconvertible into the enantiomer[8] and used as a versatile chiral building block,[9] the present transformation constitutes the determination of the absolute structure of the chiral acetate (−)-**5** as shown and an alternative synthesis of optically active oxodicyclopentadiene[3b,9,10] **8** (Scheme 3).

In conclusion, we have demonstrated that the tricyclic racemic acyloin *endo*-3-hydroxytricyclo[4.2.1.0^{2,5}]non-7-en-4-one (±)-**3** is dynamically acylated with vinyl acetate in an enantiospecific manner *via* the transient *meso*-enediol **4** in THF containing triethylamine in the presence of lipase to give the single *endo*-acetate (−)-**5**, proving itself as a potential chiral building block[2] and serving at the same time as the precursor of versatile chiral oxodicyclopentadiene **8**. We are currently working on extension of the present dynamic kinetic resolution to other acyloins having latent *meso* structure as well as to the acyloins having latent prochirality, and on exploitation of the chiral acyloin acetates obtained for the construction of a variety of optically active molecules.

Footnotes

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† The stereochemistry of **3** was determined by NOE measurements.
‡ Lipase LIP (*Pseudomonas aeruginosa*, TOYOBO) also gave the same acetate (−)-**5** (97% ee) in 60% yield without leaving the starting acyloin (±)-**3**.
§ The same compound was generated from **3** on reaction with 30% H_2O_2–0.5 M NaOH.

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