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Asymmetric Aldol Reactions of an α′-Benzoyl Titanium Enolate

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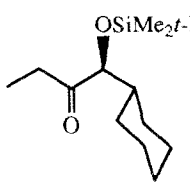
Abstract: Diastereofacial selectivities of 97–99.7% can be conveniently obtained in aldol reactions of the chiral titanium enolate derived from the ketone $C_2H_5COCH(OCOPh)$*cyclo*-C_6H_{11}, with representative aldehydes.

The triisopropoxytitanium *Z*-enolate of ketone **1** has been found to give very high diastereofacial selectivities in aldol reactions with typical aldehydes.[1,2] It therefore provides a potentially useful alternative to the corresponding dialkylboron enolate, which has been valuable in macrolide synthesis.[3–6] Subsequent studies have shown that the triisopropoxytitanium enolate of the TMS derivative **2** also gives a very high selectivity with benzaldehyde.[7] The triisopropoxytitanium *E*-enolate of a ketone related to **1** (*t*-butyl in lieu of cyclohexyl) gives very high selectivities with aliphatic aldehydes.[8–10] An alternative to such silyl enolates would be useful, as aldehydes containing inexpensively TMS-protected OH groups could then be used. Since a free OH group is produced in the aldol reaction, it would be advantageous if the original OH group could remain differentially TMS-protected during deprotection and cleavage of the chiral auxiliary group to convert the adduct into a carboxylic acid or other functional group. We have therefore investigated the use of a simple ester group, and have found that ketone **3** does provide very high diastereofacial selectivities in titanium-mediated aldol reactions with representative aldehydes. In all cases, the favored stereochemistry is the same as that observed with **1** and **2**, which is as expected from nonchelation of their silyloxy oxygens.



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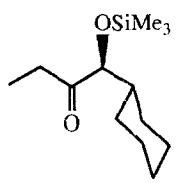

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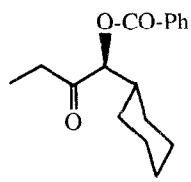

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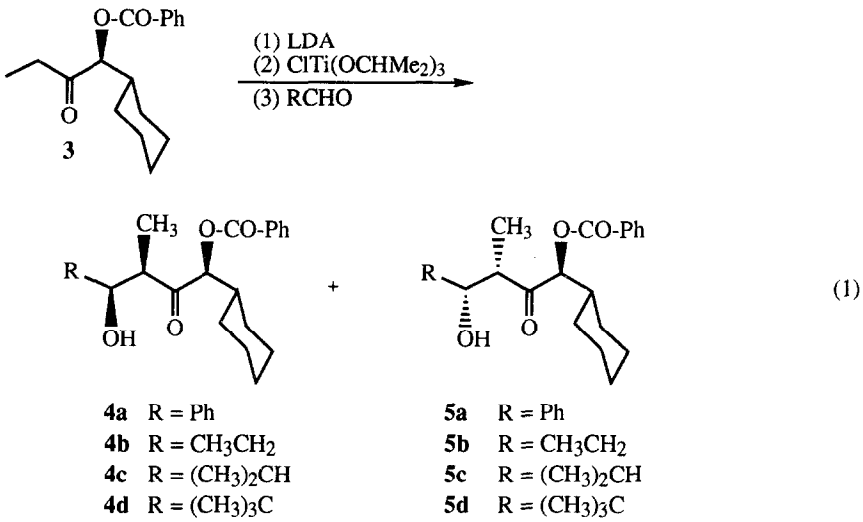
RESULTS

Aldol reactions were carried out using excess titanium, as we had previously discovered to be required for high selectivities with **1** and **2** (eq 1). Ratios of the two syn adduct diastereomers, **4** and **5**, were determined by ^{1}H NMR (500 MHz). No anti adducts could be detected. Of prime importance was assignment of the absolute configurations. Chemical conversion gave compounds which were, in all cases but one, correlated with X-ray crystal structures we had previously determined. For all aldehydes, adduct **4** was highly preferred.



(1)

4a R = Ph
4b R = CH_3CH_2
4c R = $(CH_3)_2CH$
4d R = $(CH_3)_3C$

5a R = Ph
5b R = CH_3CH_2
5c R = $(CH_3)_2CH$
5d R = $(CH_3)_3C$

Absolute Configuration of Aldol Adducts

The syn configuration of adducts **4** and **5** is shown by coupling constants $J_{C3\text{-}H,C4\text{-}H} \leq 4.8$ Hz.[11–13] In addition, adducts **4a**, **5b**, and **5d** were shown to be syn by chemical correlation with compounds whose X-ray structures had been determined by us (vide infra).

For stereochemical correlation, aldol adducts were converted to dibenzoates by treatment with benzoic acid in the presence of dicyclohexylcarbodiimide (DCC) and catalytic 4-(*N*,*N*-dimethylamino)pyridine (DMAP). Dibenzoates to be correlated were also prepared from the aldol adducts of **2**, which have been studied in this laboratory,[14] by conversion to the diol through TMS removal in methanolic HCl, followed by dibenzoylation using DCC and DMAP. The diastereomeric dibenzoates were differentiated by means of their 500-MHz ^{1}H NMR spectra.

The lithium-mediated aldol reaction of **3** with benzaldehyde gave a mixture of **4a** and **5a**, which were converted to the dibenzoates (the same two dibenzoates were also prepared from the aldol adducts of **2**[7] as described above). These dibenzoates were chromatographically separated. The dibenzoate of **4a** was crystalline; an X-ray crystal structure was performed to give its structure and stereochemistry. Adduct **5a** must then have the opposite syn stereochemistry.

The crystalline diol from aldol reaction with propionaldehyde, corresponding to **5b**, had been prepared from lithium-mediated aldol reaction of ketone **2**, and its structure and stereochemistry were determined by an X-ray crystal structure. The dibenzoate of this diol was found to be identical by 500-MHz ^{1}H NMR to the dibenzoate prepared from **5b** (and not to that from **4b**). Hence, the stereochemistry of **5b** is as shown, and adduct **4b** must have the opposite syn configuration.

Likewise, the crystalline diol from aldol reaction with pivalaldehyde, corresponding to **5d**, had been prepared from lithium-mediated aldol reaction of ketone **2**, and its structure and stereochemistry were determined by an X-ray crystal structure. The dibenzoate of this diol was identical by 500-MHz NMR to the dibenzoate prepared from **5d** (and not **4d**). Therefore, the stereochemistry of **5d** is as shown, and adduct **4d** must have the opposite syn configuration.

In each case—**4a**, **4b**, and **4d**—the *major* product from the present titanium-mediated aldol reactions of **3** was identical to the *minor* product of the lithium-mediated aldol reaction of **2**, as shown by the 500-MHz ^{1}H NMR spectra of the dibenzoates. This same result was obtained with the major adduct **4c**: its dibenzoate is identical to the dibenzoate of the minor adduct from lithium-mediated aldol reaction of ketone **2**. These results

strongly indicate, but do not prove, that the stereostructures of **4c** and **5c** correspond to those already proven for the other aldehydes, and are as shown above.

Diastereofacial Selectivities of the Titanium-Mediated Aldol Reactions

The stereochemical results found (Table 1) show that ketone **3** is capable of providing very high facial selectivities, as desired, ranging up to 99.7%. The reactions are clean and high-yield; isolated yields could be further optimized.

Table 1. Stereoselectivities in Aldol Reactions of Triisopropoxytitanium Enolate of Ketone **3** with Representative Aldehydes in THF at –78 °C

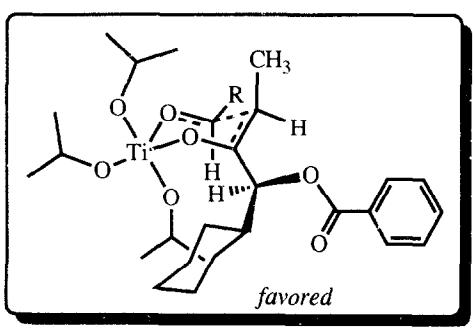
Aldehyde	Stereoselectivity, **4**:**5**	NMR Yield[a]
PhCHO	365:1	87% (70%)
CH_3CH_2CHO	32.1:1	88% (68%)
$(CH_3)_2CHCHO$	42.7:1	78% (59%)
$(CH_3)_3CCHO$	132:1	92% (68%)

[a]Yields not fully optimized; isolated yields in parentheses

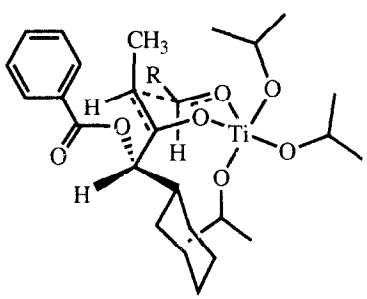
DISCUSSION

High diastereofacial selectivities are found in these titanium-mediated aldol reactions for all of the differently branched aldehydes tested. These results indicate that ketone **3** will be generally useful in giving high selectivities with most kinds of aldehydes. Since aldol reactions of such titanium enolates are convenient in terms of reagent cost and ease of workup, ketone **3** may be valuable in synthetic applications. It reaches our goal of a highly selective chiral enolate employing a group other than the hitherto studied silyloxy types (**1**, **2**), such that differential protection can be set up by use of aldehyde substrates containing silyl-protected OH groups. Thus, these experiments widen the scope of highly stereoselective aldol reactions of titanium enolates.

The absolute stereochemistries produced are all in the same sense, **4** being highly favored over **5**. This is the same sense as observed with the titanium enolates of **1** and **2**, which is most reasonably explained by a transition structure in which the chiral center is oriented to place the larger cyclohexyl group as far as possible from the cyclic aldol reaction site, with the aldehyde attacking the enolate face adjacent to the H rather than that adjacent to the $PhCO_2$– group at the chiral center. As shown in the diagrams below, **6** (which leads to **4**) would be favored relative to **7** (which leads to **5**).



6



7

In aldol reactions of the lithium enolate of **2**, the preferred product stereochemistry corresponds to **5**,[7,14] a result believed to arise from chelation of the TMSO group's oxygen to lithium in the preferred transition structure.[7–10,14,15] In order for chelation to occur, the TMSO group would have to be oriented inwards, analogously to **7** above, so that the opposite stereochemistry (as in **7**) would be preferred. The nonchelation stereochemical preference (as in **6**) is found for the titanium enolates of **1**, **2**, and now also **3**.

At this point, a chelation (or electrostatic) interaction between titanium and the benzoate carbonyl oxygen cannot be ruled out as a contributing factor to the high facial selectivities observed. Chelation involving the benzoate *carbonyl*, as opposed to *ether*, oxygen can be encompassed within a transition structure resembling **6**, with the ester group and H oriented inwards and the ester carbonyl adopting a conformation aiming toward the titanium (chelation would involve a 7-membered ring). On the other hand, chelation involving the *ether* oxygen (5-membered chelation ring) would not be favorable for stereochemistry like **6** and would be expected to prefer the opposite stereochemistry, like **7**. Certainly the data do not permit any decision on the presence or absence of benzoate carbonyl chelation, but benzoate ether-oxygen chelation is very unlikely based on the preference for **4** (expected via **6**) rather than **5** (expected via the chelated analogue of **7**).

EXPERIMENTAL

Materials and Methods. Reagents and solvents were dried and/or purified before use.[16] Diisopropylamine (DIPA) and CH_2Cl_2 were distilled from CaH_2. THF was distilled from sodium metal/benzophenone ketyl immediately prior to use. $ClTi(OCHMe_2)_3$ was distilled under reduced pressure. PhCHO was dried with anhydrous Na_2CO_3, filtered, and distilled at reduced pressure from Zn dust. CH_3CH_2CHO, $(CH_3)_2CHCHO$, and $(CH_3)_3CCHO$ were dried with $CaSO_4$, filtered and distilled immediately prior to use. Reactions and distillations were conducted under argon with oven-dried glassware (160 °C) that was flame-dried under a stream of argon.

Flash column chromatography (FCC) was carried out using Baker or Whatman silica gel (40 μm average particle size) according to the procedure of Still et al.[17] Eluent compositions follow each column description. Fractions were analyzed by TLC with visualization by either fluorescence or staining with 2.3% ethanolic phosphomolybdic acid. Glass-backed TLC plates (with fluorescence) were used for analysis of reactions and fractions. Solvent systems are described as volume:volume ratios before mixing. Rotary evaporation refers to removal of volatile components, including solvent, under water aspirator pressure at ≤ 30 °C.

All NMR spectra are reported in ppm on the δ scale relative to internal tetramethylsilane for proton and carbon NMR. Coupling constants J are given in Hz. High resolution mass spectra (CI = chemical ionization) were obtained from the University of Pennsylvania Mass Spectrometry Facility of the Chemistry Department.

Synthesis of (S)-(–)-1-Benzoyloxy-1-cyclohexylbutan-2-one (3). This chiral ketone was prepared from (*S*)-(+)-mandelic acid according to a literature procedure[4] with benzoate as the protecting group. The DCC esterification protocol was employed as follows.[18] To a flask charged with the (*S*)-(–)-1-cyclohexyl-1-hydroxybutan-2-one (510 mg, 3 mmol), benzoic acid (378 mg, 3.1 mmol), DCC (722 mg, 3.5 mmol), and DMAP (5 mg, 0.035 mmol) was added CH_2Cl_2 (8 mL). The mixture was stirred at ca. 25 °C under argon with periodic checking by TLC. After the reaction was complete, dicyclohexylurea was removed by filtration. The filtrate was washed with H_2O (7 mL × 3), 5% glacial acetic acid (7 mL × 3), and then H_2O (7 mL × 3). The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was purified by FCC (5:1 hexanes–ether) to afford pure **3** as a pale yellow oil (657 mg, 80%). FTIR ($CHCl_3$): 3028, 3020, 2933(s), 2857, 1718(s), 1620, 1452, 1265, 1220 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.08–7.42 (m, 5 H), 5.09 (d, J = 4.6, 1 H), 2.59–2.41 (m, 2 H), 1.86–0.85 (m, 11 H), 1.03 (t, J = 7.2, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 208.4, 166.2, 133.3, 129.8, 129.6, 128.5, 82.8, 39.8, 33.0, 29.6, 27.6, 26.1, 26.0, 7.1. CI MS (*m/e*): 275.1628 $(M + H)^+$, calcd for $C_{17}H_{23}O_3$ 275.1647.

General Procedure for Formation and Reaction of Titanium Enolates of (S)-(–)-1-Benzoyloxy-1-cyclohexylbutan-2-one (3). The procedure followed for generation of the lithium enolate was similar to that developed by Heathcock et al.[9] Reactions were run in a septum-capped, 25-mL, flame-dried flask under argon, and all reagents were added via oven-dried hypodermic syringes. To DIPA (1.2 equiv based on ketone **3**) in THF at 0 °C was added *n*-butyllithium solution in hexanes (1.1 equiv). After stirring for 15 min, the solution was cooled to –78 °C, ketone **3** (1.0 equiv) was added as a solution in THF dropwise over 4 min (with 3 rinsings, a total of 0.5 mL of THF), and the reaction was stirred for 1.5 h at –78 °C. The mixture turned pale yellow to bright yellow as the addition progressed.

The titanium enolate was generated from this lithium enolate by a procedure similar to that of Reetz et al.,[19] with some modifications. At –78 °C, $ClTi(OCHMe_2)_3$ (neat, 3.0 equiv based on amount of LDA added) was added dropwise with stirring.[1] The solution immediately turned dark yellow. It was allowed to warm to –30 °C over 1 h and then kept between –30 and –40 °C for 1.25 h. After cooling to –78 °C, the aldehyde (2.0 equiv) was added. The mixture was allowed to warm again to –40 °C over 1.5 h and then kept between –40 and –50 °C for 2 h. The reaction was quenched with the addition of saturated, aqueous NH_4F (0.5 mL). After warming to ca. 25 °C, the mixture was extracted with diethyl ether three times. The organic layers were washed with saturated, aqueous NaCl and dried with $MgSO_4$. The solvent was removed by rotary evaporation, and the crude oil was placed on a vacuum pump (ca. 0.05 mmHg) for at least 2 h. The reactions described below were run on a 0.27 mmol scale.

(1S,3R,4R)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3-methyl-4-phenylbutan-2-one (4a). The aldol condensation was carried out with **3** (75 mg, 273 μmol) and PhCHO according to the general procedure at a concentration of 0.138 M. The ratio of diastereomers was determined by ^1H NMR analysis of the crude product (500 MHz, $CDCl_3$, *CH*OH), δ **4a** = 5.19 (d, *J* = 3.5), **5a** = 5.32 (d, *J* = 4.3), giving **4a**:**5a** = 365:1. Purification by FCC (7:3 hexanes–ether, R_f = 0.326) gave a colorless oil, **4a** (73 mg, 70%). FTIR ($CHCl_3$): 3610(br), 2934(s), 2857, 1713(s), 1603, 1452, 1280, 1223, 1117 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.05–7.21 (m, 10 H), 5.19 (d, *J* = 3.5, 1 H), 5.05 (d, *J* = 4.9, 1 H), 3.04 (qd, *J* = 7.0, 4.8, 1 H), 2.93 (br s, 1 H, disappears on D_2O exchange), 1.86–0.85 (m, 11 H), 1.26 (d, *J* = 7.2, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 214.6, 166.0, 141.8, 133.4, 129.8, 129.5, 128.5, 128.3, 127.6, 126.3, 81.6, 73.2, 49.8, 38.8, 30.2, 26.9, 26.3, 26.1, 25.8, 11.7. CI MS (*m/e*): 381.2079 $(M + H)^+$, calcd for $C_{24}H_{29}O_4$ 381.2066.

(1S,3R,4S)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3-methylhexan-2-one (4b). Enolization of **3** (75 mg, 273 μmol) and condensation with CH_3CH_2CHO were carried out according to the general procedure at a concentration of 0.084 M. The ratio of diastereomers was determined by ^1H NMR analysis of the crude product (500 MHz, $CDCl_3$, *CH*O_2C), δ **4b** = 5.26 (d, *J* = 3.8), **5b** = 5.23 (d, *J* = 3.8), giving **4b**:**5b** = 32.1:1. Purification by FCC (7:3 hexanes–ether, R_f = 0.35) gave a colorless oil, **4b** (62 mg, 68%). FTIR ($CDCl_3$): 3528(br), 2935(s), 2857, 1710.6(s), 1602, 1452, 1278, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.07–7.44 (m, 5 H), 5.26 (d, *J* = 3.8, 1 H), 3.76 (tdd, *J* = 5.0, 2.7, 2.5, 1 H), 2.86 (d, *J* = 2.5, 1 H, disappears on D_2O exchange), 2.77 (qd, *J* = 7.2, 2.7, 1 H), 2.05–1.14 (series of m, 13 H), 1.23 (d, *J* = 7.1, 3 H), 0.89 (t, *J* = 7.2, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 212.4, 166.0, 133.4, 129.8, 129.5, 128.5, 81.7, 72.3, 46.0, 39.2, 30.1, 27.4, 26.7, 26.3, 26.1, 25.9, 10.4, 9.9. CI MS (*m/e*): 333.2022 $(M + H)^+$, calcd for $C_{20}H_{29}O_4$ 333.2066.

(1S,3R,4S)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3,5-dimethylhexan-2-one (4c). Enolization of **3** (73 mg, 266 μmol) and condensation with $(CH_3)_2CHCHO$ were carried out according to the general procedure at a concentration of 0.084 M. The ratio of diastereomers was determined by ^1H NMR analysis of the crude product mixture.(500 MHz, $CDCl_3$, *CH*OH), δ **4c** = 3.42 (dd, *J* = 8.5, 2.4), **5c** = 3.71 (dd, *J* = 8.8, 3.0), giving **4c**:**5c** = 42.7:1. Purification by FCC (7:3, hexanes–ether, R_f = 0.38) gave a colorless oil, **4c** (55 mg, 59%). FTIR ($CDCl_3$): 3523(br), 2935(s), 2857, 1710(s), 1452, 1279, 1110 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ

8.06–7.44 (series of m, 5 H), 5.26 (d, J = 4.0, 1 H), 3.42 (dd, J = 8.5, 2.4, 1 H), 2.95 (superimposed s and qd, J = 7.2, 2.5, 2 H), 2.01 (m, 1 H), 1.80–1.20 (series of m, 12 H), 1.21 (d, J = 7.2, 3 H), 0.96 (d, J = 6.6, 3 H), 0.77 (d, J = 6.8, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 212.7, 166.0, 133.4, 129.8, 129.5, 128.5, 81.7, 76.0, 43.6, 39.4, 30.3, 30.1, 27.5, 26.3, 26.1, 25.9, 19.1, 19.0, 9.6. CI MS (*m/e*): 364.2523 $(M + NH_4)^+$, calcd for $C_{21}H_{34}NO_4$ 364.2488.

*(1S,3R,4R)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3,5,5-trimethylhexan-2-one (**4d**).* Aldol condensation was carried out with **3** (73 mg, 266 μmol) and $(CH_3)_3CCHO$ according to the general procedure at a concentration of 0.138 M. The ratio of diastereomers was determined by ^{1}H NMR analysis of the crude product mixture (500 MHz, $CDCl_3$, $(CH_3)_3C$), δ **4d** = 0.899 (s), **5d** = 0.974 (s), giving **4d**:**5d** = 132:1. Purification by FCC (4:1 hexanes–ether, R_f = 0.44) gave a colorless oil, **4d** (71 mg, 68%). FTIR ($CDCl_3$): 3534(br), 2935(s), 2857, 1711(s), 1602, 1452, 1280, 1135, 1112, 996 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07–7.43 (series of m, 5 H), 5.28 (d, J = 3.9, 1 H), 3.49 (br s, 1 H), 3.06 (qd, J = 7.2, 1.5, 1 H), 2.62 (d, J = 2.7, 1 H), 2.05–1.11 (series of m, 11H), 1.24 (d, J = 7.2, 3 H), 0.89 (s, 9 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 212.4, 166.0, 133.4, 129.8, 128.6, 81.5, 76.7, 42.4, 39.3, 35.4, 30.1, 27.6, 26.9, 26.3, 25.9, 11.2. CI MS (*m/e*): 361.2358 $(M + H)^+$, calcd for $C_{22}H_{33}O_4$ 361.2379.

Dibenzoates for Assignment of Absolute Configurations of the Aldol Products

As described in the Results section, the aldol adducts from ketone **3** were benzoylated with benzoic acid, DCC, and catalytic DMAP to give dibenzoates, which were then identified by NMR comparison with the dibenzoates prepared by desilylation and dibenzoylation of corresponding adducts from ketone **2**. In each case, the dibenzoates of both syn diastereomers were available from the lithium-mediated aldol reaction of **2**, so that it was rigorously known which of these diastereomers was the product of the titanium-mediated aldol reaction of ketone **3**. Substantial differences exist in both the ^{1}H and ^{13}C NMR spectra of the dibenzoate diastereomer pairs. Characterization of the dibenzoates of **4a–4d**, the predominant adducts formed in the present titanium-mediated aldol reactions of **3**, is described below.

*Dibenzoate of (1S,3R,4R)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3-methyl-4-phenylbutan-2-one (**4a**).* White solid, mp 143 °C. FTIR (CH_2Cl_2): 2934(s), 2857, 1722(s), 1602, 1585, 1494, 1451, 1316, 1275, 1112, 1070, 1026, 957, 923 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05–7.2 (series of m, 15 H), 6.21 (d, J = 9.5, 1 H), 5.14 (d, J = 2.6, 1 H), 3.54–3.30 (m, 1 H), 1.68–0.05 (m, 11 H), 1.47 (d, J = 7.0, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 206.1 165.9, 165.3, 139.2, 133.2, 133.1, 129.8, 129.7, 129.6, 128.5, 128.43, 128.4, 128.3, 127.5, 81.3, 76.7, 49.7, 30.5, 26.4, 26.1, 26.0, 25.8, 15.2. CI MS: (*m/e*): 485.2336 $(M + H)^+$, calcd for $C_{31}H_{33}O_5$ 485.2328.

X-ray crystal structure analysis of this dibenzoate was performed by Dr. P Carroll, Director of the Chemistry Department X-ray Crystallography Facility. The crystal structure demonstrates that the stereochemistry of this dibenzoate, and hence that of **4a**, is as shown for **4a** above.

*Dibenzoate of (1S,3S,4S)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3-methyl-4-phenylbutan-2-one (**5a**).* A mixture of the dibenzoates of **4a** and **5a** was prepared from aldol reaction of the lithium enolate of **3**.[14] Preparative TLC separation (2:1 hexanes–ether) provided the pure dibenzoate of **5a**: Colorless, viscous oil. FTIR (CH_2Cl_2): 2933(s), 2856, 1723(s), 1603, 1493, 1452, 1316, 1248, 1136, 1111, 1071, 1026, 996 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79–7.02 (series of m, 15 H), 6.30 (d, J = 7.6, 1 H), 5.25 (d, J = 5.4, 1 H), 3.85–3.48 (m, 1 H), 1.80–0.05 (series of 5m, 11 H), 1.20 (d, J = 6.9, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 207.4, 165.7, 165.4, 138.8, 133.4, 133.1, 130.1, 129.9, 129.7, 129.5, 128.6, 128.4, 128.2, 127.1, 81.8, 76.4, 48.6, 39.1, 29.7, 29.4, 27.3, 25.9, 25.9, 13.2. CI MS: (*m/e*): 485.2375 $(M + H)^+$, calcd for $C_{31}H_{33}O_5$: 485.2328.

*Dibenzoate of (1S,3R,4S)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3-methylhexan-2-one (**4b**).* Colorless oil. FTIR (CH_2Cl_2): 3075, 2936, 2857, 1719(s), 1602, 1452, 1316, 1248, 1113, 1071, 1026, 996, 938 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.08–7.38 (series of 6 m, 10 H), 5.37 (d, J = 3.4, 1 H), 5.30 (m, 1 H), 3.22 (m, 1 H), 2.07–1.04 (series of m, 13 H), 1.27 (d, J = 7.1, 3 H), 0.86 (t, J = 7.2, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 207.8, 166.1, 165.8, 133.3, 132.9, 132.2, 130.2, 129.8, 129.6, 128.5, 128.3, 81.7, 75.8, 45.8, 39.1, 30.2, 26.9, 26.2, 25.92, 25.90, 25.2, 13.0, 10.0. CI MS: (*m/e*): 437.2306 $(M + H)^+$, calcd for $C_{27}H_{33}O_5$ 437.2328.

*Dibenzoate of (1S,3R,4S)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3,5-dimethylhexan-2-one (**4c**).* Viscous oil. FTIR ($CDCl_3$): 2970(s), 2933, 2857, 2258, 1718(s), 1603, 1452, 1315, 1272, 1177, 1113, 1070, 1026, 996, 941 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.10–7.39 (series of 6 m, 10 H), 5.49 (d, J = 3.4, 1 H), 5.35 (dd, J = 6.6, 5.4, 1 H), 3.27–3.0 (m, 1 H), 2.14–0.91 (series of m, 12 H), 1.21 (d, J = 7.0, 3 H), 0.89 (d, J = 6.7, 3 H), 0.87 (d, J = 6.9, 3 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 208.1, 166.0, 165.8, 133.4, 132.9, 129.8, 129.7, 129.6, 128.5, 128.3, 81.7, 77.5, 44.1, 39.5, 30.2, 30.1, 27.1, 26.3, 26.1, 25.9, 19.8, 17.1, 12.4. CI MS (*m/e*): 451.2495 $(M + H)^+$, calcd for $C_{28}H_{35}O_5$ 451.2484.

*Dibenzoate of (1S,3R,4R)-1-Benzoyloxy-1-cyclohexyl-4-hydroxy-3,5,5-trimethylhexan-2-one (**4d**).* Viscous oil. FTIR ($CDCl_3$): 2932, 2857, 2359, 2341, 1719(s), 1603, 1452, 1315, 1272, 1136, 1112, 1026, 997, 927 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.09–7.25 (series of 6 m, 10 H), 5.55 (d, J = 3.4, 1 H), 5.45 (d, J = 5.9, 1 H), 3.23–3.18 (m, 1 H), 2.2–0.91 (series of m, 11 H), 1.17 (d, J = 7.2, 3 H), 0.9 (s, 9 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 207.9, 165.9, 133.4, 132.8, 130.3, 129.8, 129.7, 129.5, 128.6, 128.3, 81.8, 77.9, 42.1, 39.5, 35.9, 30.0, 27.2, 26.5, 26.3, 26.1, 25.9, 13.0. CI MS: (*m/e*): 465.2693 $(M + H)^+$, calcd for $C_{29}H_{37}O_5$: 465.2641.

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