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The 1,4-addition of organometallic reagents to enoates derived from pinanediol

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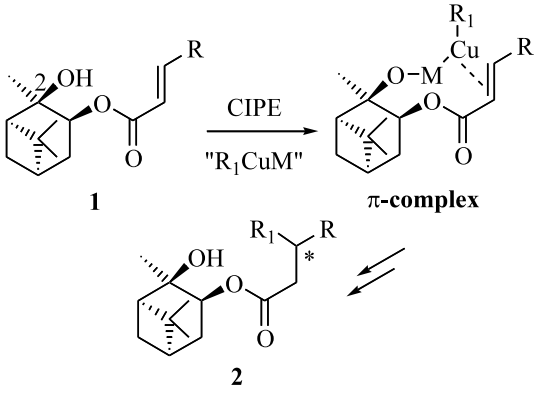
Abstract—The complex-induced, proximity effect-promoted 1,4-addition of $RCu{\cdot}BF_3$ and R_2CuLi to enoates derived from (−)-pinanediol leads to adducts with the opposite sense of chirality (up to 98% d.e.). © 2002 Published by Elsevier Science Ltd.

The stereoselective 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds has been widely employed for asymmetric carbon–carbon bond formation. Although the enantioselective approaches based on asymmetric catalysis have enjoyed a surge in popularity,[1] the use of chiral auxiliaries attached to the enoate moiety remains an attractive method for the diastereoselective 1,4-addition of the Gilman cuprate R_2CuLi, as well as $RCu{\cdot}BF_3$ and $RMgBr/Cu^I$ reagents to chiral enoates.[2,3]

Some commercially unavailable cyclic diols have been used as chiral auxiliaries in 1,4-addition of organometallic reagents to enoates (up to 88% d.e.).[4] In these cases the diastereoselectivities can be explained by the 'complex-induced proximity effect' (CIPE).[5]

Some time ago we described chiral auxiliaries derived from (−)-pinanediol in asymmetric α-alkylation and aldol reactions.[6] Herein, we report the use of this structurally rigid and readily available diol as a chiral auxiliary for the CIPE-promoted 1,4-addition of $RCu{\cdot}BF_3$ and R_2CuLi to the enoates **1** (Scheme 1). The CIPE arises from chelation between the oxygen at the 2 position of **1** and the metal (M) followed by complexation of copper with the double bond leading to a π-complex. The π-facial stereoselection in the conjugate addition produces the 1,4-adducts **2**.

Reaction of crotonyl chloride and cinnamoyl chloride with (−)-pinanediol (cat. DMAP, CH_2Cl_2, Et_3N, rt, 24 h)[7,8] led to the chiral enoates **1a** and **1b** in yields of 50 and 65%, respectively (Table 1).[9,10] The 1,4-addition reactions to **1a** and **1b** were carried out following typical procedures.[4h,11] While the treatment of **1a** with *n*-$BuCu{\cdot}BF_3$ (10 equiv.) led to the adduct **2a** in high stereoselectivity (entry 1), the use of *n*-Bu_2CuLi (5 equiv.) gave the opposite isomer **3a** in the same selectivity (entry 2).[12,13] The additions of both *n*-$BuCu{\cdot}BF_3$ and *n*-Bu_2CuLi to the less reactive enoate **1b** produced a mixture of **2b** and **3b** with a deleterious effect on the



Scheme 1. CIPE-promoted 1,4-addition of R_1CuM to the enoate **1**.

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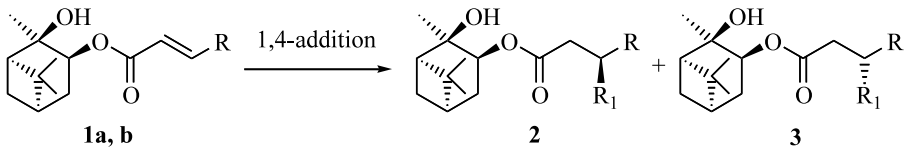
Table 1. Stereoselectivities in the conjugate additions to the enoates **1a**,**b**



1a, b **2** **3**

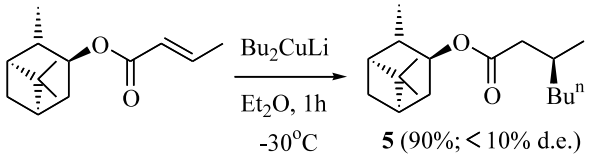
Entry	1	R	1,4-Addition[a]	Adducts	Yield (%)[b]	2:3[c]
1	**a**	CH_3	*n*-BuCu·BF_3, Et_2O, −30°C, 3 h	**a**	65	99:1
2	**a**	CH_3	*n*-Bu_2CuLi, Et_2O, −30°C, 1 h	**a**	90	1:99
3	**b**	Ph	*n*-BuCu·BF_3, Et_2O, −30°C, 3 h	**b**	50	73:27
4	**b**	Ph	*n*-Bu_2CuLi, Et_2O, −30°C, 1 h	**b**	85	25:75
5	**a**	CH_3	Ph_2CuLi, Et_2O, −30°C, 1 h	**c**	85	30:70[d]
6	**a**	CH_3	CH_3NO_2, DBU, CH_3CN, rt, 24 h	**d**	75	ND (35% d.e.)[e]
7	**b**	Ph	CH_3NO_2, DBU, CH_3CN, rt, 72 h	**e**	65	ND (32% d.e.)[e,f]

[a] Reactions were performed using 2 mmol of enoates **1a**,**b**.
[b] Yields for the purified mixture of adducts **2a**–**e** and **3a**–**e**.
[c] By the signals for the C=O in the ^{13}C NMR spectra unless noted.
[d] By the signals of the CH_3 groups in the ^1H NMR spectra at 300 MHz.
[e] The major isomer, **2** or **3**, was not determined.
[f] % d.e. by the signal of the CH_2 adjacent to the C=O in the ^{13}C NMR.

stereoselectivity (entries 3 and 4).[14] Moderate selectivity was obtained in the 1,4-addition of Ph_2CuLi to **1a** and the mixture of adducts **2c** and **3c** was not separated (entry 5).[15] According to a previous report in the literature for addition of Me_2CuLi to an enoate derived from diol,[4c] the reaction of **1b** with both BuCu·BF_3 and Me_2CuLi was not successful. The addition of the anion derived from nitromethane[16] to **1a** led to mixture of the adducts **2d** and **3d** in low stereoselectivity (entry 6)[17] and this tendency was also observed for the mixture of the adducts **2e** and **3e** (entry 7).[18] In both cases the absolute configurations of the major isomers were not determined. The low stereoselectivities obtained from entries 6 and 7 can be attributed to the absence of the CIPE-promoted 1,4-addition since the anion produced from CH_3NO_2 and DBU cannot be coordinated by the oxygen in position 2 of **1a**,**b**.

The addition *n*-Bu_2CuLi to the enoate **4**, which was prepared from (+)-isopinocampheol (crotonic acid, DCC, cat. DMAP, CCl_4, rt, 96 h, 35%) gave the adduct **5** with low selectivity (Scheme 2).[19–21] This reaction also showed an opposite sense of chirality in comparison to the additions of *n*-Bu_2CuLi and Ph_2CuLi to **1a**,**b**, showing the importance of the hydroxyl group in **1a**,**b** for the CIPE-promoted reaction.

The signals in the ^1H NMR spectra of the mixture of **2b** and **3b** are too close together for determining the

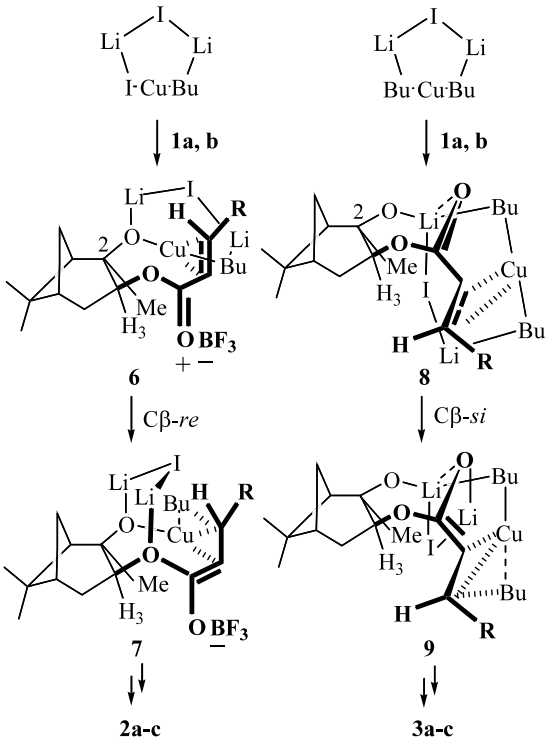


Scheme 2. Low stereoselectivity in 1,4-addition to the enoate **4**.

diastereomeric ratio, so the selectivity of this reaction was obtained from the relative intensities of the signals of the C=O groups in quantitative ^{13}C NMR spectrum of the isomeric mixture using the 'gated decoupled' procedure.

The absolute configurations of the newly created centers in the isomers **2a**,**b** and **3a**–**c** were determined by hydrolysis (aq. KOH, EtOH, reflux, 3 h) of each isomeric mixture to the known (*S*)-(−)-3-methylheptanoic acid (75% yield), (*S*)-(+)-3-phenylbutyric acid (93% yield) and (*R*)-(−)-3-phenyl-heptanoic acid (95% yield), respectively.[4c,22]

A possible stereochemical pathway to produce the adducts **2a**,**b** and **3a**–**c** is proposed in Scheme 3. As *n*-Bu_2CuLi and *n*-BuCu·BF_3 were prepared in Et_2O from *n*-BuLi and CuI, they can exist as a mixed cyclic cluster, *n*-Bu_2CuLi·LiI and a six-centered cluster, *n*-BuCu·2LiI, respectively.[23] The CIPE is proposed to arise from the coordination of the lithium of these clusters by the oxygen in the position 2 of the enoates **1a** and **1b**. In the additions of *n*-BuCu·BF_3 both enoates **1a** and **1b** react in their *s-trans* conformations leading to the π-complex **6**, where the carbonyl group adopts a *syn*-periplanar relationship to H_3.[23,24] Similarly to the 1,4-addition of mixed cuprates having a dummy ligand,[23a,25] we can assume an additional coordination of copper with the oxygen at C-2 and the CIPE-promoted 1,4-addition would occur mainly from the Cβ-*re* face of **6** leading to transition state **7**. In the reactions with *n*-Bu_2CuLi and Ph_2CuLi the enoates **1a** and **1b** react in their *s*-trans conformations leading to the π-complex **8**.[23] In this intermediate the *O*–Li bond length (1.92–2.00 Å) allows the formation of a seven-membered ring (where lithium is coordinated by the carbonyl oxygen), which adopts an anticlinal relationship to H_3. This would allow Cβ-*si* attack leading to the transition state **9**.



Scheme 3. Possible pathways for 1,4-addition to the enoates **1a**,**b**.

In summary, this first report on the use of (–)-pinanediol as a chiral auxiliary for 1,4-addition reactions shows that cuprate reagents such as R_2CuLi and $RCu{\cdot}BF_3$ lead to an opposite sense of stereochemistry in the CIPE-promoted reaction, thus allowing the formation of adducts with different configurations simply by changing the nucleophile.

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9. Enoate **1a**: Pale yellow oil. $[\alpha]_D^{25}$ +4.9 (*c* 1, $CHCl_3$). IR (neat, cm^{-1}): 3600–3300, 3010, 2988, 2914, 1714, 1653, 1441, 1375, 1185, 1014. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.04 (dq, 15.6 Hz, 6.9 Hz, CH), 5.94 (dq, 15.4 Hz, 1.5 Hz, CH), 5.20 (dd, 9.6 Hz, 5.4 Hz, H-3), 2.60–2.46 (m, H-4β and OH), 2.29–2.17 (m, H-7β), 2.01 (t, 5.7 Hz, H-5), 1.98–1.94 (m, H-1), 1.89 (dd, 6.8 Hz, 1.5 Hz, CH_3), 1.67 (ddd, 14.1 Hz, 5.4 Hz, 2.4 Hz, H-4α), 1.54 (d, 10.5 Hz, H-7α), 1.31 (s, CH_3), 1.29 (s, CH_3), 1.01 (s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 165.5 (C-1′), 145.3 (C-3′), 122.3 (C-2′), 73.8 (C-2), 71.3 (C-3), 54.0 (C-1), 40.2 (C-5), 38.5 (C-6), 34.7 (C-4), 29.7 (CH_3), 27.5 (CH_3), 28.1 (C-7), 24.2 (CH_3), 17.9 (CH_3). MS (70 eV, *m*/*z*): 221 (10), 152 (25), 126 (61), 109 (42), 99 (91), 83 (28), 71 (73), 69 (100). Calcd for $C_{14}H_{22}O_3$: 70.56% C, 9.30% H. Found: 70.88% C, 9.14% H.
10. **Enoate 1b**: White solid, mp 47–48°C. $[\alpha]_D^{25}$ +5.1 (*c* 0.33, CH_2Cl_2). IR (KBr, cm^{-1}): 3600–3400, 3013, 2978, 2918, 1723, 1706, 1639, 1337, 1311, 1182, 1167, 1143, 711, 684. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.75 (d, 16.2 Hz, CH); 7.59–7.52 (m, $2H_{arom.}$), 7.44–7.37 (m, $3H_{arom.}$), 6.53 (d, 15.9 Hz, CH), 5.30 (dd, 9.6 Hz, 5.4 Hz, H-3), 2.63–2.52 (m, H-4β), 2.34–2.24 (m, H-7β), 2.02 (t, 5.5 Hz, H-5), 2.20–1.95 (m, H-1), 1.78 (ddd, 13.8 Hz, 5.6 Hz, 2.4

Hz, H-4α), 1.56 (d, 10.5 Hz, H-7α), 1.38 (s, CH_3), 1.32 (s, CH_3), 1.05 (s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 166.1(C-1′), 145.2 (C-3′), 134.1($C_{arom.}$), 130.3, 128.8 and 128.0 ($C_{arom.}$), 117.6 (C-2′); 73.9 (C-2), 71.7 (C-3), 54.0 (C-1), 40.3 (C-5), 38.6 (C-6), 34.5 (C-4), 29.8 (CH_3), 28.1 (CH_3), 27.7 (C-7), 24.1 (CH_3). MS (70 eV, m/z): 300 (M^+, 8), 169 (17), 152 (21), 131 (100), 126 (30), 103 (49), 99 (66), 71 (57). HREIMS calcd for $C_{19}H_{24}O_3$ (M^+): 300.3520. Found: 300. 3642.

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12. **Adduct 2a**: 98% d.e.: Pale yellow oil. $[\alpha]_D^{25}$ −1.6 (*c* 0.64, CH_2Cl_2). IR (neat, cm^{-1}): 3620–3360, 2929, 2847, 1748, 1458, 1372. ^1H NMR (300 MHz, $CDCl_3$, ppm): 5.16 (dd, 9.6 Hz, 5.7 Hz, H-3); 2.55–2.45 (m, H-4β), 2.39 (dd, 14.6 Hz, 6.3 Hz, H-2′), 2.26–2.20 (m, H-7β), 2.20 (dd, 14.7 Hz, 8.1 Hz, H-2′), 2.01 (t, 5.4 Hz, H-5), 1.97–1.94 (m, H-1), 1.63 (ddd, 13.9 Hz, 5.7 Hz, 2.1 Hz, H-4α), 1.50 (d, 10.5 Hz, H-7α), 1.30 (s, CH_3), 1.29 (s, CH_3), 1.27–1.23 (m, H-3′-H-6′), 1.01 (s, CH_3), 0.97 (d, 6.6 Hz, CH_3), 0.90 (t, 6.3 Hz, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 172.2 (C-1′), 73.5 (C-2), 71.3 (C-3), 53.9 (C-1), 41.8 (C-2′), 40.2 (C-5), 38.4 (C-6), 36.2, 28.9 and 22.6 (C-4′-C-6′), 34.6 (C-4), 30.3 (C-3′), 29.6 and 27.7 (CH_3), 28.0 (C-7), 24.0 (CH_3), 19.5 (CH_3), 13.9 (CH_3). MS (70 eV, m/z): 169 (15), 152 (30), 135 (32), 127 (67), 126 (57), 109 (41), 108 (33), 99 (100), 93 (50), 85 (37), 71 (57), 69 (38), 57 (85), 55 (41). Calcd for $C_{18}H_{32}O_3$: 72.94% C, 10.88% H. Found: 73.18% C, 10.54% H.
13. **Adduct 3a**: 98% d.e.: Pale yellow oil. $[\alpha]_D^{25}$ +0.9 (*c* 1.72, CH_2Cl_2). IR (neat, cm^{-1}): 3620–3360, 2923, 2851, 1739, 1455, 1370. ^1H NMR (300 MHz, $CDCl_3$, ppm): 5.16 (dd, 9.6 Hz, 5.4 Hz, H-3), 2.56–2.45 (m, H,4β), 2.39 (dd, 14.4 Hz, 6.0 Hz, H-2′), 2.29–2.21 (m, H,7β), 2.19 (dd, 14.5 Hz, 8.0 Hz, H-2′), 2.01 (t, 5.7 Hz, H-5), 1.98–1.91 (m, H-1), 1.63 (ddd, 14.1 Hz, 5.6 Hz, 2.3 Hz, H-4α), 1.49 (d, 10.8 Hz, H-7α), 1.31 (s, CH_3), 1.29 (s, CH_3), 1.32–1.22 (m, H-3′-H-6′), 1.01 (s, CH_3), 0.96 (d, 6.2 Hz, CH_3), 0.92 (t, 6.0 Hz, CH_3). MS (70 eV, m/z) 296 (M^+, 3), 169 (21), 135 (27), 127 (56), 126 (45), 109 (32), 99 (100), 93 (57), 85 (29), 71 (48), 69 (53), 57 (80). HREIMS calcd for $C_{18}H_{32}O_3$ (M^+): 296.3975. Found: 296.4117.
14. **Mixture of adducts 2b and 3b**: Pale yellow oil. $[\alpha]_D^{25}$ +18.6 (*c* 5.44, CH_2Cl_2) for **2b**:**3b** = 73:27 and $[\alpha]_D^{25}$ −4.5 (*c* 1.97, CH_2Cl_2) for **2b**:**3b** = 25:75. IR (neat, cm^{-1}): 3615–3330, 3021, 2944, 2915, 2862, 1732, 1635, 1448, 1371, 1262, 1161, 773, 698. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.35–7.18 (m, $H_{arom.}$), 5.00 (dd, 9.4 Hz, 5.6 Hz, H-3 of **3b**), 4.99 (dd, 9.5 Hz, 5.9 Hz, H-3 of **2b**), 3.13–3.05 (m, H-3′), 2.76–2.62 (m, H-2′), 2.41–2.31 (m, H-4β), 2.21–2.12 (m, H,7β), 1.94–1.85 (m, H-1 and H-5), 1.72–1.60 (m, CH_2), 1.47 (ddd, 14.2 Hz, 6.1 Hz, 2.5 Hz, H-4α), 1.41 (d, 10.5 Hz, H-7α), 1.36–1.10 (m, 2×CH_2), 1.24 (s, CH_3), 1.13 (s, CH_3 of **3b**), 0.96 (s, CH_3 of **2b**), 0.94 (s, CH_3), 0.83 (t, 6.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 171.6 (C-1′ of **2b**), 171.3 (C-1′ of **3b**), 143.8 ($C_{arom.}$ of **3b**), 143.6 ($C_{arom.}$ of **2b**), 128.4 ($C_{arom.}$ of **2b**), 128.3 ($C_{arom.}$ of **3b**), 127.3 ($C_{arom.}$ of **2b**), 127.2 ($C_{arom.}$ of **3b**), 126.6 ($C_{arom.}$ of **2b**), 126.4 ($C_{arom.}$ of **3b**), 73.4 (C-2 of **3b**), 73.2 (C-2 of **2b**), 71.5 (C-3 of **3b**), 71.3 (C-3 of **3b**), 53.9 (C-1 of **3b**), 53.7 (C-1 of **2b**), 42.8 (C-3′ of **2b**), 42.1 (C-3′ of **3b**), 42.0 (C-2′ of **2b**), 41.4 (C-2′ of **3b**), 40.2 (C-5 of **2b**), 40.1 (C-5 of **3b**), 38.4 (C-6), 36.4 (CH_2 of **3b**), 36.3 (CH_2 of **2b**), 34.4 (C-4 of **2b**), 34.3 (C-4 of **3b**), 28.2 (C-7 of **2b**), 28.0 (C-7 of **3b**), 29.3 and 22.4 (CH_2), 29.4, 27.7 and 24.0 (CH_3), 13.8 (CH_3). MS (70 eV, m/z): 358 (M^+,18), 341 (100), 340 (33), 283 (29), 189 (56), 147 (98), 126 (37), 99 (30), 91 (73). HREIMS calcd for $C_{24}H_{34}O_3$ (M^+): 358.4720. Found: 358.4518.
15. **Mixture of adducts 2c and 3c**: 40% d.e.: Pale yellow oil. $[\alpha]_D^{25}$ +9.8 (*c* 0.44, CH_2Cl_2). IR (neat, cm^{-1}): 3612–3290, 3027, 2963, 2923, 2871, 1733, 1452, 1374, 1267, 1164, 1018, 764, 701. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.35–7.18 (m, $H_{arom.}$), 5.04 (dd, 9.7 Hz, 4.5 Hz, H-3 of **2c**), 5.03 (dd, 9.6 Hz, 5.7 Hz, H-3 of **3c**), 3.34–3.24 (m, H-3′), 2.70 (dd, 16.7 Hz, 8.7 Hz, H-2′ of **3c**), 2.69 (dd, 13.5 Hz, 7.2 Hz, H-2′ of **2c**), 2.44–2.31 (m, H-4β), 2.22–2.14 (m, H-7β), 1.95–1.84 (m, H-1 and H-5), 1.51 (ddd, 13.9 Hz, 5.8 Hz, 2.4 Hz, H-4α), 1.41 (d, 10.3 Hz, H-7α of **3c**), 1.40 (d, 10.5 Hz, H-7α of **2c**), 1.34 (d, 7.2 Hz, CH_3 of **3c**), 1.32 (d, 6.9 Hz, CH_3 of **2c**), 1.25 (s, CH_3), 1.16 (s, CH_3 of **2c**), 1.05 (s, CH_3 of **3c**), 0.94 (s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 170.8 (C-1′ of **3c**), 170.5 (C-1′ of **2c**), 144.6 ($C_{arom.}$ of **2c**), 144.4 ($C_{arom.}$ of **3c**), 127.9 ($C_{arom.}$ of **3c**), 127.8 ($C_{arom.}$ of **2c**), 126.0 ($C_{arom.}$ of **3c**), 125.9 ($C_{arom.}$ of **2c**), 125.8 ($C_{arom.}$ of **3c**), 125.7 ($C_{arom.}$ of **2c**), 72.8 (C-2 of **2c**), 72.6 (C-2 of **3c**), 70.9 (C-3 of **2c**), 70.8 (C-3 of **3c**), 53.2 (C-1 or C-5 of **2c**), 53.1 (C-1 or C-5 of **3c**), 42.4 (C-2′ of **3c**), 42.0 (C-2′ of **3c**), 39.5 (C-1 or C-5 of **3c**), 39.4 (C-1 or C-5 of **2c**), 37.8 (C-6), 36.5 (C-3′ of **3c**), 35.8 (C-3′ of **2c**), 33.9 (C-4 of **3c**), 33.8 (C-4 of **2c**), 28.8 (CH_3 of **2c**), 28.7 (CH_3 of **3c**), 27.5 (C-7 of **3c**), 27.4 (C-7 of **2c**), 27.1(CH_3 of **3c**), 27.0 (CH_3 of **2c**), 23.3 (CH_3), 21.6 (CH_3). Calcd for $C_{20}H_{28}O_3$: 75.92% C, 8.92% H. Found: 75.74% C, 9.44% H.
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17. **Mixture of adducts 2d and 3d**: 35% d.e.: Yellow oil. $[\alpha]_D^{25}$ −4.44 (*c* 11, CH_2Cl_2). IR (neat, cm^{-1}): 3650–3300, 2922, 2871, 1731, 1551, 1454, 1379, 1181, 1011, 901. ^1H NMR (300 MHz, $CDCl_3$, ppm): 5.17 (dd, 9.6 Hz, 5.4 Hz, H-3), 4.53 (dd, 16.2 Hz, 6.3 Hz, H-4′ of the minor isomer), 4.51 (dd, 16.3 Hz, 7.8 Hz, H-4′ of the major isomer), 4.41 (dd, 16.2 Hz, 7.8 Hz, H-4′ of the major isomer), 4.39 (dd, 16.1 Hz, 6.6 Hz, H-4′ of the minor isomer), 2.88–2.77 (m, H-3′), 2.58–2.41 (m, H-2′ and H-4β), 2.30–2.22 (m, H-7β), 2.02–1.95 (m, H-1 and H-5), 1.69 (ddd, 9.1 Hz, 5.0 Hz, 2.3 Hz, H-4α), 1.44 (d, 10.5 Hz, H-7α of the minor isomer), 1.43 (d, 10.5 Hz, H-7α of the major isomer), 1.34 (s, CH_3), 1.29 (s, CH_3), 1.14 (d, 6.6 Hz, CH_3), 0.99 (s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 169.9 (C-1′ of the minor isomer), 169.8 (C-1′ of the major isomer), 79.5 (C-4′ of the minor isomer), 79.4 (C-4′ of the major isomer), 73.3 (C-2), 71.7 (C-3 of the major isomer), 71.6 (C-3 of the minor isomer), 53.7 (C-1 or C-5 of the major isomer), 53.6 (C-1 or C-5 of the minor isomer), 39.7 (C-1 or C-5 of the minor isomer), 39.6 (C-1 or C-5 of the major isomer), 38.1 (C-6), 34.0 (C-4), 37.5 (C-2′ of the major isomer), 37.4 (C-2′ of the minor isomer), 29.0 (CH_3), 28.9 (C-3′ of the major isomer), 28.8 (C-3′ of the minor isomer), 27.3 (C-7 of the major isomer), 27.2 (C-7 of the minor isomer), 27.0 (CH_3), 23.4 (CH_3), 16.7 (CH_3). MS (70 eV, m/z): 299 (M^+, 9), 144 (14), 126 (27), 113 (28), 99 (100), 71 (40), 69 (29). HREIMS calcd for $C_{15}H_{25}NO_2$ (M^+): 299.1733. Found: 299.1827.

18. **Mixture of adducts 2e and 3e**: 32% d.e.: Yellow oil. $[\alpha]_D^{25}$ −2.63 (*c* 8, CH_2Cl_2). IR (neat, cm^{-1}): 3620–3340, 3033, 2988, 2921, 2871, 1734, 1554, 1454, 1379, 1270, 1163, 1083, 766, 701. ^1H NMR (300 MHz, $CDCl_3$, ppm): 7.39–7.25 (m, $H_{arom.}$), 5.07 (dd, 9.8 Hz, 5.1 Hz, H-3 of the minor isomer), 5.06 (dd, 9.8 Hz, 5.4 Hz, H-3 of the major isomer), 4.80–4.61 (m, H-4′), 4.08–3.96 (m, H-3′), 2.87 (dd, 8.8 Hz, 7.8 Hz, H-2′), 2.43–2.30 (m, H-4β), 2.50–2.16 (m, H-7β), 1.96–1.87 (m, H-1 and H-5), 1.83 (OH), 1.51 (ddd, 8.8 Hz, 5.2 Hz, 2.4 Hz, H-4α), 1.38 (d, 10.2 Hz, H-7α of the major isomer), 1.35 (d, 10.5 Hz, H-7α of the minor isomer), 1.26 (s, CH_3), 1.20 (s, CH_3 of the minor isomer), 1.12 (s, CH_3 of the major isomer), 0.94 (s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 169.8 (C-1′), 138.0 ($C_{arom.}$ of the minor isomer), 137.9 ($C_{arom.}$ of the major isomer), 129.0 ($CH_{arom.}$), 128.2 ($C_{arom.}$ of the major isomer), 128.1 ($C_{arom.}$ of the minor isomer), 127.3 ($C_{arom.}$ of the major isomer), 127.2 ($C_{arom.}$ of the minor isomer), 79.6 (C-4′ of the minor isomer), 79.4 (C-4′ of the major isomer), 73.6 (C-2 of the minor isomer), 73.5 (C-2 of the major isomer), 72.3 (C-3 of the minor isomer), 72.2 (C-3 of the major isomer), 54.0 (C-1 or C-5 of the minor isomer), 53.9 (C-1 or C-5 of the major isomer), 40.5 (C-3′), 40.2 (C-1 or C-5 of the minor isomer), 40.1 (C-1 or C-5 of the major isomer), 38.5 (C-6), 38.0 (C-2′ of the major isomer), 37.6 (C-2′ of the minor isomer), 34.3 (C-4 of the major isomer), 34.2 (C-4 of the minor isomer), 29.4 (CH_3), 27.9 (C-7 of the major isomer), 27.8 (C-7 of the minor isomer), 27.6 (CH_3 of the major isomer), 27.5 (CH_3 of the minor isomer), 24.0 (CH_3). MS (70 eV, *m*/*z*): 361 (M^+, 4), 282 (11), 135 (40), 130 (39), 126 (30), 99 (100), 71 (31). HREIMS calcd for $C_{20}H_{27}NO_5$ (M^+): 361.1889. Found: 361.2072.

19. **Enoate 4**: Pale yellow oil. $[\alpha]_D^{25}$ +34.7 (*c* 0.62, CH_2Cl_2). IR (neat, cm^{-1}): 2911, 1718, 1659, 1447, 1375, 1307, 1265, 1183, 1155, 1101, 1008, 969, 838, 666. ^1H NMR (300 MHz, $CDCl_3$, ppm): 6.96 (dq, 15.5 Hz, 6.8 Hz, H-3′), 5.86 (dq, 15.5 Hz, 1.5 Hz, H-2′), 5.10 (ddd, 9.5 Hz, 5.0 Hz, 4.2 Hz, H-3), 2.65–2.55 (m, H-4β), 2.42–2.33 (m, H-7β), 2.20–2.10 (m, H-2), 1.97–1.80 (m, H-1 and H-5), 1.88 (dd, 6.9 Hz, 1.8 Hz, CH_3), 1.69 (ddd, 14.3 Hz, 4.0 Hz, 3.0 Hz, H-4α), 1.23 (s, CH_3), 1.11 (d, 7.5 Hz, CH_3), 1.08 (d, 9.6 Hz, H-7α), 0.98 (s, CH_3). ^{13}C NMR ($CDCl_3$, ppm): 166.5 (C-1′), 144.0 (C-3′), 123.3 (C-2′), 78.7 (C-3), 47.4 and 41.2 (C-1 and C-5), 43.7 (C-2), 38.2 (C-6), 35.9 (C-4), 33.4 (C-7), 27.4 (CH_3), 23.7 (CH_3), 20.4 (CH_3), 17.9 (CH_3). MS (70 eV, *m*/*z*): 222 (M^+, 1), 167 (18), 149 (55), 137 (89), 93 (67), 81 (100), 71 (56), 69 (67), 57 (85), 56 (74). HREIMS calcd for $C_{14}H_{22}O_2$ (M^+): 222.1619. Found: 222.1807.

20. **Adduct 5**: <10% d.e.: Pale yellow oil. $[\alpha]_D^{25}$ +50 (*c* 0.02, CH_2Cl_2). IR (neat, cm^{-1}): 2972, 2930, 2872, 1732, 1466, 1378, 1153, 729, 666. ^1H NMR (300 MHz, $CDCl_3$, ppm): 5.09–5.02 (m, H-3), 2.64–2.54 (m, H-4β), 2.41–2.32 (m, H-7β), 2.31–2.20 (m, H-2′), 2.18–2.06 (m, H-2), 1.70–1.50 (m, H-1, H-4α and H-5), 1.48–1.40 (m, H-3′), 1.35–1.20 (m, H-4′-H-6′), 1.23 (s, CH_3), 1.05 (d, 9.9 Hz, H-7α), 0.97 (s, CH_3), 0.94 (d, 6.6 Hz, CH_3 of 3*S*-isomer), 0.93 (d, 6.5 Hz, CH_3 of 3*R*-isomer), 0.91 (t, 6.9 Hz, CH_3 of 3*S*-isomer), 0.89 (t, 6.6 Hz, CH_3 of 3*R*-isomer). MS (70 eV, *m*/*z*): 280 (M^+, 2), 185 (41), 137 (100), 136 (81), 127 (64), 121 (37). HREIMS calcd for $C_{18}H_{32}O_2$ (M^+): 280.2402. Found: 280.2560.

21. The stereoselectivity was determined from the relative intensities of the signals due to the methyl groups at 0.91 and 0.89 ppm in the crude ^1H NMR spectra.

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