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Tetrahedron Letters 47 (2006) 4929–4932
Tetrahedron Letters

Direct one-pot highly enantioselective assembly of polyketide and carbohydrate synthons

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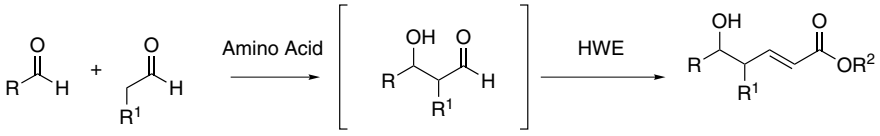
Received 13 March 2006; revised 23 April 2006; accepted 4 May 2006
Available online 26 May 2006

Abstract—A short, direct, catalytic, enantioselective synthesis of polyketide segments and carbohydrates is presented. The novel, direct, one-pot, organocatalytic asymmetric tandem cross-aldol/Horner–Wittig–Emmons reactions assemble polyketide and carbohydrate derivatives in good yield with 93–98% ee. The one-pot catalytic asymmetric tandem reaction was applied to a highly enantioselective formal de novo synthesis of the rare carbohydrate, L-altrose.

The rapidly growing development of glycobiology and carbohydrate based pharmaceuticals demands the increased development of reaction design and method advancement for the selective construction of natural and unnatural carbohydrates.[1] In this context, the de novo synthesis of carbohydrates is of immense importance.[2,3] However, most conventional monosaccharide syntheses start from the chiral pool and involve multiple steps and require protective group strategies and subsequent reduction–oxidation steps.[4] The reduction of protective group strategies can be accomplished by the use of enzymes as catalysts for the highly selective de novo synthesis of carbohydrates[5] and polyketide natural products.[6] Organocatalysis is a rapidly expanding research field within asymmetric catalysis.[7] Most recently, amino acid catalysis was added to the repertoire of carbohydrate synthesis.[8] Inspired by Nature's ability to assemble complex molecules from simple precursors in an asymmetric and economic fashion,[6] we have begun a research programme that focuses on the development of biomimetic, catalytic, asymmetric, one-pot and tandem reactions.[9,10] Based on retrosynthetic analyses, we envisioned that a one-pot, direct, asymmetric, tandem aldol-Horner–Wittig–Emmons (HWE) sequence would be an excellent catalytic entry for the enantioselective synthesis of polyketide and carbohydrate derivatives (Eq. 1).



(1)

Herein, we describe a novel, direct, one-pot, organocatalytic asymmetric aldol-HWE reaction that yields polyketide and carbohydrate derivatives in good yield with 93–98% ee.

In an initial experiment, propionaldehyde (2 mmol) was added to a stirred solution of (*S*)-proline (10 mol %) in DMF (0.5 mL). After 15 h of vigorous stirring at 4 °C, the temperature was increased to room temperature and LiBr (1.5 mmol), methyl 2-(diethoxyphosphoryl)-acetate (1.5 mmol) and DBU (228 mg, 1.5 mmol) were added to the reaction mixture. After stirring for 4 h at room temperature, the reaction mixture was passed directly through a silica gel column to give the pure natural product mycinonic acid ester **2a** in 52% yield with 2.3:1 dr (*anti*:*syn*) and 93% ee (Eq. 2).[11,12]

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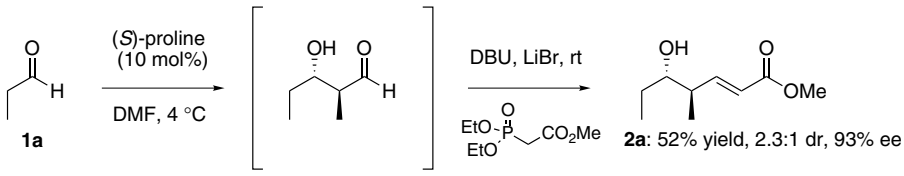
doi:10.1016/j.tetlet.2006.05.018



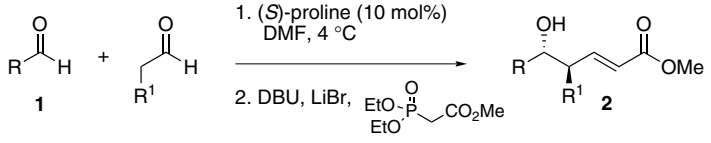
(2)

Encouraged by this result, we investigated the one-pot direct organocatalytic asymmetric tandem aldol/HWE reaction with a set of different aldehydes **1** as substrates (Table 1).

The direct one-pot catalytic asymmetric reactions proceeded smoothly and were highly chemo- and enantioselective. For instance, the catalytic enantioselective reactions with acceptor aldehydes **1b** and **1c** gave the corresponding α,β-unsaturated-δ-hydroxy esters **2b** with an 11:1 dr and 96% ee, and **2c** with a 10:1 dr and 98% ee, respectively.[13] Thus, the reactions with aldehydes **1b** and **1c** as acceptors were slightly more stereoselective as compared to the reaction with propionaldehyde **1a**. The *δ*-hydroxytriketide products **2** are useful synthons for the synthesis of polyketide macrolactones. Moreover, the direct one-pot organocatalytic asymmetric reaction was also performed with α-benzyloxyacetaldehyde **1d** as the donor to give carbohydrate derivative **2d** in 60% yield with a 4:1 dr and 98% ee.[14] In order to show further the synthetic utility of the amino acid-catalyzed one-pot direct asymmetric tandem cross-aldol/HWE reaction, carbohydrate derivative **2d** was converted in one step, with high diastereoselectivity, to altronic acid **3d** with a 98% ee by catalytic dihydroxylation (Scheme 1).[15,16] Thus, the novel catalytic one-pot reaction is a direct asymmetric entry to altronic acid derivatives. Next, altronic acid **3d** was converted to the corresponding altronic δ-lactone **4d**. Subsequent dibenzylation furnished perbenzylated δ-lactone **4d′** and comparison of the optical rotation ($[\alpha]_D^{25}$ +10.1 (*c* 0.6, $CHCl_3$); literature: $[\alpha]_D^{24}$ +14.3 (*c* 1.01, $CHCl_3$)[16]) with the literature established that L-altronic acid δ-lactone **4d′** had been assembled in an asymmetric fashion by (*S*)-proline catalysis.[17] Hence, the stereochemical outcome is in accordance with previous (*S*)-proline catalyzed direct cross-aldol reactions.[8]

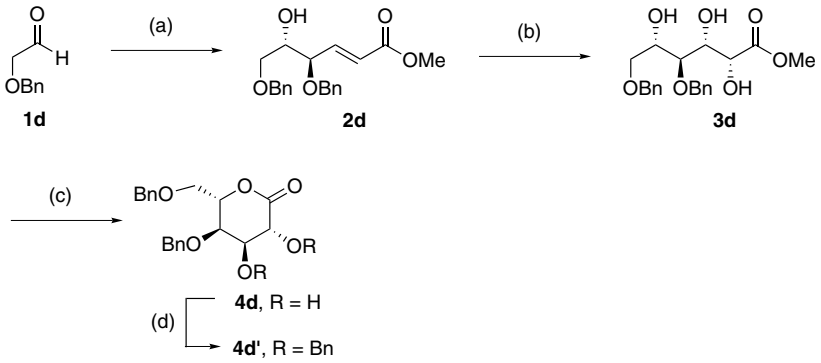
Furthermore, we performed a two-step, organocatalytic, asymmetric, self-aldol, Wittig sequence that gave isomer

Table 1. One-pot, direct, organocatalytic, asymmetric, tandem cross-aldol/HWE reactions

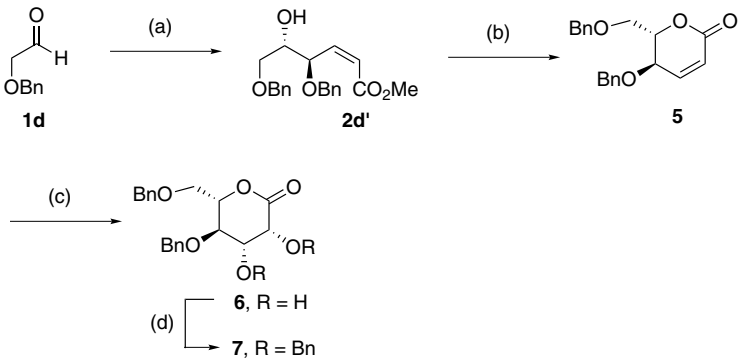


Entry	R	R^1	Product	Yield[a] (%)	dr[b]	ee[c] (%)
1	Et	Me	**2a**	52	2.3:1	93
2	*i*-Pr	Me	**2b**	58	11:1	96
3	*c*-Hexyl	Me	**2c**	59	10:1	98
4	CH_2OBn	OBn	**2d**	60[d]	4:1	98

[a] Isolated yield of pure product **2** after silica gel column chromatography.
[b] Determined by NMR analyses.
[c] Determined by chiral phase GC or HPLC analyses.
[d] The whole reaction sequence was performed at room temperature.



Scheme 1. Reagents and conditions: (a) cat. (*S*)-proline, aldehyde **1d**, DMF, 4 °C, 48 h then $(EtO)_2POCH_2COOMe$, LiCl, DBU, rt, 60% for **2d**; (b) cat. OsO_4, NMO, acetone–H_2O 1:1, rt, 74% for **3d** >19:1 dr; (c) cat. CF_3COOH, CH_2Cl_2, rt, 80% for **4d**; (d) BnBr, *n*-Bu_4NI, NaH, THF, rt, 56% for **4d′**.



Scheme 2. Reagents and conditions: (a) (i) cat. (*S*)-proline, aldehyde **1d**, DMF, rt, 48 h; (ii) $(Ph)_3PCHCOOMe$, MeOH, rt; (b) cat. *p*-TsOH, CH_2Cl_2, rt, 51% (three steps) for **5**, 3:1 dr (trans:cis 3:1), 97% ee; (c) cat. OsO_4, NMO, acetone–H_2O 1:1, rt, 60% for **6** >19:1 dr; (d) BnBr, *n*-Bu_4NI, NaH, THF, rt, 50% for **7**.

2d′ in a 3:1 (*Z*:*E*) ratio with 3:1 dr and 97% ee (Scheme 2).

Lactonization in the presence of *p*-toluenesulfonic acid gave δ-lactone **5** in a 51% overall yield (three steps) with 97% ee.[18] Highly diastereoselective dihydroxylation (>19:1 dr)[15] afforded mannoic acid δ-lactone **6** that was dibenzylated to give the corresponding perbenzylated carbohydrate **7**.[19,20] Comparison of the optical rotation $[\alpha]_D^{25}$ −1.0 (*c* 0.1, $CHCl_3$); literature: *ent*-**7** $[\alpha]_D^{24}$ +0.37 (*c* 0.1, $CHCl_3$)[17] and the NMR data of **7** to the literature confirmed that L-mannoic δ-lactone is furnished by (*S*)-proline catalysis.[20]

In summary, we have developed a direct organocatalytic tandem asymmetric cross-aldol-HWE reaction. The reaction proceeds with excellent chemo- and enantioselectivity and furnishes polyketide and carbohydrate derivatives in good yield with up to 10:1 dr and 93–98% ee. Moreover, altronic acid and mannoic δ-lactone with 98% and 97% ee, respectively, were synthesized by subsequent highly diastereoselective catalytic dihydroxylation. Thus, the combination of biomimetic one-pot catalytic asymmetric reactions and diastereoselective catalytic dihydroxylation is a direct route to carbohydrate derivatives.

Acknowledgements

A.C. thanks the Swedish Research Council, Carl-Trygger and Hierta Foundation, for financial support.

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F., III *J. Org. Chem.* **2002**, *67*, 301; (m) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798; (n) Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 3949.

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11. Compound **2a**: $[\alpha]_D^{25}$ +10.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (t, $J = 7.6$ Hz, 3H), 1.09 (d, $J = 7.2$ Hz, 3H), 1.36–1.45 (m, 1H), 1.50–1.57 (m, 1H), 1.74 (br s, 1H), 2.39–2.45 (m, 1H), 3.43–3.48 (m, 1H), 3.72 (s, 3H), 5.86 (d, $J = 16.0$ Hz, 1H), 6.96 (dd, $J = 16.0$, 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 16.0, 27.6, 42.4, 51.6, 76.3, 121.6, 151.2, 167.3. The ee was determined on acetylated **2a**: Chiral GC: 93% ee, CP-Chirasil-DexCB column, temperature programme: 95 °C, hold 3 min, 95–120 °C, rate: 2 °C/min, hold 3 min, 120–200 °C, rate: 80 °C/min, hold 5 min major isomer: $t_R = 16.67$ min; minor isomer: $t_R = 17.81$ min.
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13. To a stirred solution of (*S*)-proline (12 mg, 10 mol %) and isobutyraldehyde (144 mg, 2 mmol) in DMF (1 mL), propionaldehyde (58 mg, 1 mmol) was added slowly over 42 h at +4 °C. Next, the reaction mixture was allowed to reach room temperature and LiBr (217.5 mg, 2.5 mmol), methyl 2-(diethoxyphosphoryl)acetate (525 mg, 2.5 mmol) and DBU (380 mg, 2.5 mmol) were added. After 4 h of stirring at room temperature, the reaction mixture was passed through a silica gel FC column (ethyl acetate/pentane = 1:7) to give the pure product **2b** as a clear oil (108 mg, 58%). Compound **2b**: $[\alpha]_D^{25}$ 12.7 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, $J = 6.6$ Hz, 6H), 1.09 (d, $J = 6.9$ Hz, 3H), 1.67–1.75 (m, 1H), 2.50–2.58 (m, 1H), 3.19 (t, $J = 6.0$ Hz, 1H), 3.73 (s, 3H), 5.88 (dd, $J = 15.9$, 0.9 Hz, 1H), 7.01 (dd, $J = 15.9$, 9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7, 17.0, 19.4, 30.9, 39.8, 51.4, 79.7, 121.4, 151.0, 167.0. The ee was determined on acetylated **2b**: Chiral GC: 96% ee, CP-Chirasil-DexCB column, Temperature programme: 95 °C, hold 3 min, 95–120 °C, rate: 1.2 °C/min, hold 3 min, 120–200 °C, rate: 80 °C/min, hold 5 min, major isomer: $t_R = 22.47$ min; minor isomer: $t_R = 23.66$ min.
    Compound **2c**: $[\alpha]_D^{25}$ +13.3 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.10 (d, $J = 6.8$ Hz, 3H), 1.04–1.87 (br m, 11H), 2.56–2.60 (m, 1H), 3.20–3.23 (m, 1H), 3.73 (s, 3H), 5.87 (d, $J = 16.0$ Hz, 1H), 7.01 (dd, $J = 16.0$, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.1, 26.1, 26.4, 26.6, 27.9, 29.8, 39.3, 41.0, 51.7, 79.4, 121.8, 151.1, 167.2. Chiral GC: 97% ee, CP-Chirasil-DexCB column, temperature programme: 110 °C, hold 6.5 min, 110–160 °C, rate: 2 °C/min, hold 6.5 min, 160–200 °C, rate: 80 °C/min, hold 5 min, major isomer: $t_R = 35.259$ min; minor isomer: $t_R = 34.954$ min.
14. Compound **2d**: $[\alpha]_D^{25}$ −5.1 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 10H), 6.98 (dd, $J = 16.0$, 6.8 Hz, 1H), 6.09 (d, $J = 15.6$ Hz, 1H), 4.61 (d, $J = 11.6$ Hz, 1H), 4.51 (s, 2H), 4.39 (d, $J = 12.0$ Hz, 1H), 4.08 (t, $J = 8.4$ Hz, 1H), 3.93–3.90 (m, 1H), 3.76 (s, 3H), 3.59–3.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 70.5, 71.9, 72.4, 73.6, 78.7, 123.9, 127.97, 128.04, 128.1, 128.5, 128.60, 128.64, 137.7, 137.9, 145.1, 166.4; HPLC: 98% ee (Daicel Chiralpak AD, *i*-hexane/*i*-PrOH = 96:4, flow rate: 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 81.06$ min; minor isomer: $t_R = 72.00$ min.
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16. Compound **3d**: $[\alpha]_D^{25}$ −9.2 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.62–3.70 (m, 3H), 3.80 (s, 3H), 4.05–4.13 (m, 2H), 4.49–4.71 (m, 5H), 7.25–7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.9, 70.8, 70.9, 73.0, 73.8, 73.9, 74.4, 78.0, 128.2, 128.2, 128.3, 128.7, 128.8, 137.7, 138.0, 174.2.
17. Compound **4d′**: $[\alpha]_D^{25}$ +10.1 (*c* 0.6, $CHCl_3$); literature: $[\alpha]_D^{24}$ +14.3 (*c* 1.01, $CHCl_3$) Takahashi, H.; Hitomi, Y.; Iwai, Y.; Ikegami, S. *J. Am. Chem. Soc.* **2000**, *122*, 2995. All the spectroscopic data were identical to Takahashi et al. ^1H NMR (300 MHz, $CDCl_3$): δ 3.64–3.70 (m, 2H), 3.99–4.05 (m, 1H), 4.12 (dd, $J = 6.9$, 3.6 Hz, 1H), 4.37–4.41 (m, 2H), 4.51–4.59 (m, 4H), 4.63 (d, $J = 11.7$ Hz, 1H), 4.74 (d, $J = 11.7$ Hz, 1H), 4.86 (d, $J = 12.0$ Hz, 1H), 5.05 (d, $J = 12.0$ Hz, 1H), 7.17–7.32 (m, 20H).
18. Compound **5**: $[\alpha]_D^{25}$ −34.5 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.40–7.20 (m, 10H), 6.83 (dd, $J = 10.8$, 1.8 Hz, 1H), 5.96 (dd, $J = 10.8$, 1.2 Hz, 1H), 4.66–4.45 (m, 6H), 3.89 (dd, $J = 10.8$, 2.7 Hz, 1H), 3.73 (dd, $J = 10.8$, 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 146.5, 137.8, 137.2, 128.8, 128.7, 128.5, 128.3, 128.1, 128.0, 120.8, 80.3, 73.8, 72.5, 69.0, 68.2. HPLC: 97% ee (Daicel Chiralpak AD, *i*-hexane/*i*-PrOH = 96:4, flow rate: 0.5 mL/min, $\lambda = 254$ nm): major isomer: $t_R = 40.28$ min; minor isomer: $t_R = 44.71$ min.
19. Compound **6**: $[\alpha]_D^{25}$ −70.9 (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 2.81 (br s, 1H), 3.34 (br s, 1H), 3.69–3.78 (m, 2H), 4.04–4.08 (m, 2H), 4.41–4.46 (m, 2H), 4.50–4.52 (m, 2H), 4.55–4.67 (m, 2H), 7.25–7.37 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.7, 68.1, 69.5, 71.9, 72.3, 73.8, 79.5, 128.0, 128.2, 128.4, 128.6, 128.7, 128.9, 137.1, 137.8, 172.8.
20. Compound **7**: $[\alpha]_D^{25}$ −1 (*c* 0.1, $CHCl_3$); literature, *ent*-**7**: $[\alpha]_D^{25}$ +0.37 (*c* 0.1, $CHCl_3$), Mahmud, T.; Tornus, I.; Egelkrout, E.; Wolf, E.; Uy, C.; Floss, H. G.; Lee, S. *J. Am. Chem. Soc.* **1999**, *121*, 6973. All the spectroscopic data were identical to Mahmud et al. ^1H NMR (300 MHz, $CDCl_3$): δ 3.67–3.76 (m, 3H), 3.89–3.92 (m, 1H), 3.97–4.00 (m, 1H), 4.18–4.21 (m, 1H), 4.38–4.42 (m, 2H), 4.51 (s, 2H), 4.61–4.71 (m, 2H), 4.83 (d, $J = 12.0$ Hz, 1H), 4.97 (d, $J = 12.0$ Hz, 1H), 7.17–7.32 (m, 20H).