DOI: 10.1002/adsc.200600491

Amino Alcohols in Organocatalysed Acylation and Deacylation: The Effect of Dialkylamino Substituents on the Rate

Ludger A. Wessjohann[a,*] and Mingzhao Zhu[a]

[a] Leibniz Institute of Plant Biochemistry, Weinberg 3, 06120 Halle (Saale), Germany
Fax: (+49)-345-5582-1309; e-mail: wessjohann@ipb-halle.de

Received: September 27, 2006; Revised: September 19, 2007; Published online: November 23, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

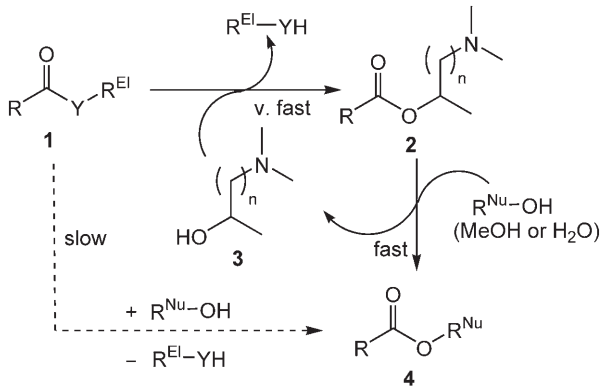
Abstract: In alcohols and esters, a neighbouring dialkylamino group can enhance the reactivity towards acylation and deacylation, respectively, that is, such amino alcohols can act as transacylation catalysts like DMAP. This effect is dependent on the number of (carbon) spacer atoms, flexibility of the molecule and the presence and position of further heteroatoms. Based on this effect, the site selective acylation and deacylation of desmycosin, a macrocycle antibiotic possessing an amino sugar moiety, is described.

Keywords: amino alcohols; amino sugars; desmycosin; organocatalysis; acylation; transesterification

Introduction

Amino alcohols are very common structures in nature and as ligands for catalysis, especially for the asymmetric addition of organozinc reagents to ketones and aldehydes.[1] However, they can also serve as catalysts in their own right, that is, without any metal ion. The basis for this claim lies in singular observations of the reactivity of hydroxy groups neighbouring tertiary amino groups (commonly in the β-position). It has been suggested that amino alcohols may be employed as serine protease mimics,[2] with the aim to achieve non-enzyme-catalysed transesterification. Selected amino alcohols were tested as candidates, exhibiting similar effects as the well studied DMAP and its recently developed derivatives.[3,4] In a noteworthy example, Sammakia et al.[4d] incorporated electron-withdrawing groups in proximity to the hydroxy group of (chiral) amino alcohols to increase their acyl transfer ability. These amino alcohols have been applied to catalyse the kinetic resolution of α-acetoxy-*N*-acyloxazolidinethiones and α-amino acid derivatives.[4e,f]

A general catalytic cycle of an amino alcohol catalyst **3** is shown in Scheme 1. The hydroxy group of **3** is activated by forming a hydrogen bond with the nitrogen which acts as a general base, imitating the function of a histidine imidazole in serine proteases.[5] With enhanced nucleophility, the hydroxy group, a mimic of the serine hydroxy group, is transacylated with substrate **1** to readily form the amino ester **2**. Due to the neighbouring effect of the amino (or ammonium) group, intermediate **2** has an increased susceptibilty to hydrolysis or alcoholysis, to finally generate an acid or ester **4**, respectively. The uncatalysed conversion from **1** to **4** may also occur (indicated by the dashed arrow) as a background reaction, but is comparably slow.



Scheme 1.

Although it has been widely accepted for the first catalytic step that the hydroxy group of **3** attacks the acyl donor **1** directly, an alternative mechanism was proposed by H. M. R. Hoffmann et al.[6] in the acylation of two β-dialkylamino alcohols, Quincorine® and Quincoridine®. They suggested that initially the tertiary amino group attacks the activated acyl donor, forming an ammonium cation intermediate. The acyl

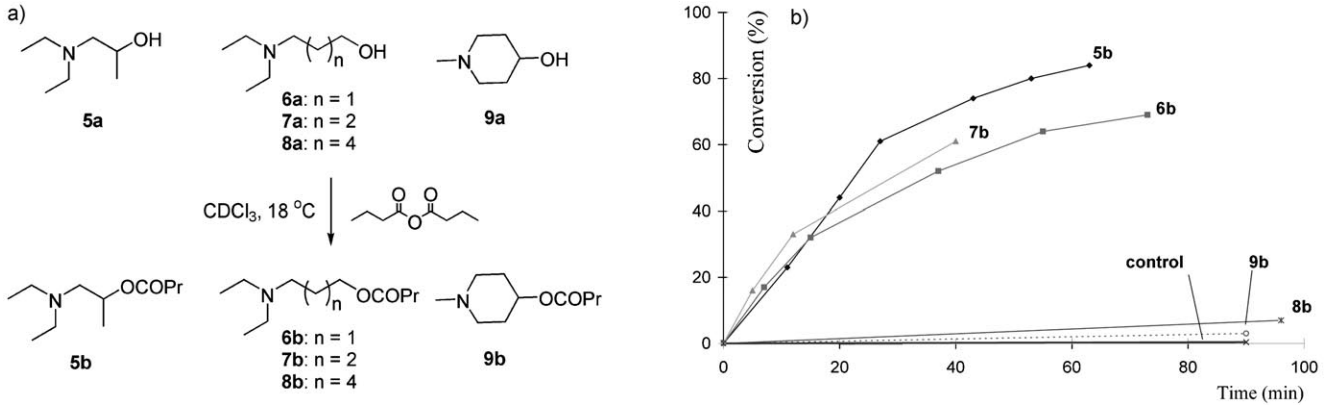


Figure 1. Acylation of amino alcohols influenced by spatial effects (18 °C, in $CDCl_3$; control: 1:1 mixture of 2-propanol/triethylamine).

group is subsequently transferred to the neighbouring hydroxy group. A similar mechanism was proposed by Waddell et al. in their acylation of quinine derivatives.[7] This N→O acyl transfer mechanism is – in principle – known from the intermolecular acylation catalysis found with DMAP which utilises an sp^2-hybridised nitrogen activated by a conjugated dimethylamino group.

Even though several amino alcohols have been applied in acyl transfer reactions in some specialised cases, no systematic structure-activity relationship studies have been performed to pave the way for the development of more general organocatalysts of this type. Herein we present a series of detailed kinetic studies of the influence of structural and electronic factors on the acylation and deacylation rates of amino alcohols.

Results and Discussion

First, the influence of the carbon tether between the amino and hydroxy group on the acylation rate was probed, and the importance of the spatial arrangement of these crucial functions, based on the flexibility of the carbon skeleton. Four acyclic diethylamino alcohols **5a**–**8a** with increasing carbon spacers and one cyclic γ-amino alcohol **9a** were chosen as substrates. Butyric anhydride was used as the acyl donor and the reaction progress was monitored by ^{1}H NMR in $CDCl_3$. A control reaction of unconnected amine and alcohol (a mixture of 2-propanol, triethylamine, and butyric anhydride) was also executed. As depicted in Figure 1, the reaction rates of **5a**–**7a** with less than five carbons are almost equal. There appears to be no notable difference in acylation rate between the secondary and the primary alcohol. With increasing spacer length, the reaction rate drops rapidly and the nitrogen almost has no apparent inductive effect if connected by a six-atom tether (*cf.* **8a/b**). Although **7a** and **9a** are both γ-amino alcohols, the latter reacts very slowly due to the fact that the rather rigid ring system restricts a proper positioning or movement of the amino group relative to the hydroxy group. Meanwhile, the conversion rate of the control reaction is undetectable within the given time, indicating that there is no noteworthy *intermolecular* base-catalysed transfer or that it proceeds very slowly.

To explore the steric effect of the amino substituent, the acylations of diethylamino alcohol **5a** and dibenzylamino alcohol **10a** with butyric anhydride were compared (Figure 2). The acylation speed of **10a** was impeded significantly by the bulkier dibenzyl substitution, but was still faster than the control reaction, which finally became visible in this prolonged experiment (NB! The scale of Figure 2 *vs.* Figure 1 is days *vs.* minutes, respectively).

In an attempt to find out whether the presence of an additional heteroatom can enhance the activity of the amino alcohols, three cyclohexane *trans*-β-amino alcohols **11a**–**13a** were synthesised.[8] Their acylation rate with butyric anhydride is shown in Figure 3. Interestingly, the reactivity of **12a** and **13a** was inhibited by the extra oxygen and nitrogen atoms due to electronic effects and, in contrast to intuitive expectations, the more basic piperazinyl derivative were the least active one in this series.

As depicted in Scheme 1, the alcoholysis (or hydrolysis) of amino ester/amide intermediates **2** is also accelerated by neighbouring amino groups, a necessary requirement for a useful catalytic cycle. In the assumption that the amino group might aid the deprotonation of the incoming final nucleophile (alcohol or water), a survey of the pH-dependence of this process was conducted. For example, ester **14b** was methanolysed in buffer solutions (MeOH/aqueous buffer/THF = 2/1/0.5) at pH values ranging from 4 to above 9. Initially, no significant differences of the reaction rates were observed within a large pH range around pH 7, indicating that the methanolysis of the amino

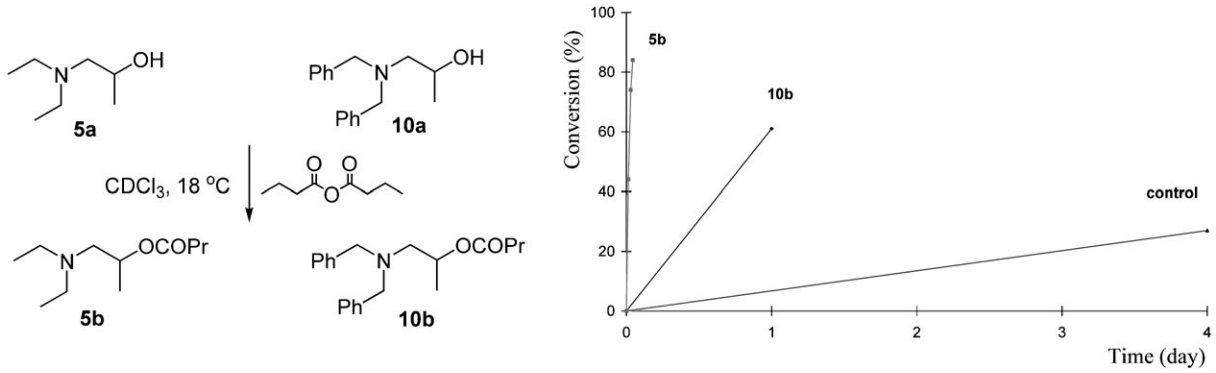


Figure 2. Acylation of amino alcohols influenced by steric effect (control: 1:1 mixture of 2-propanol/triethylamine).

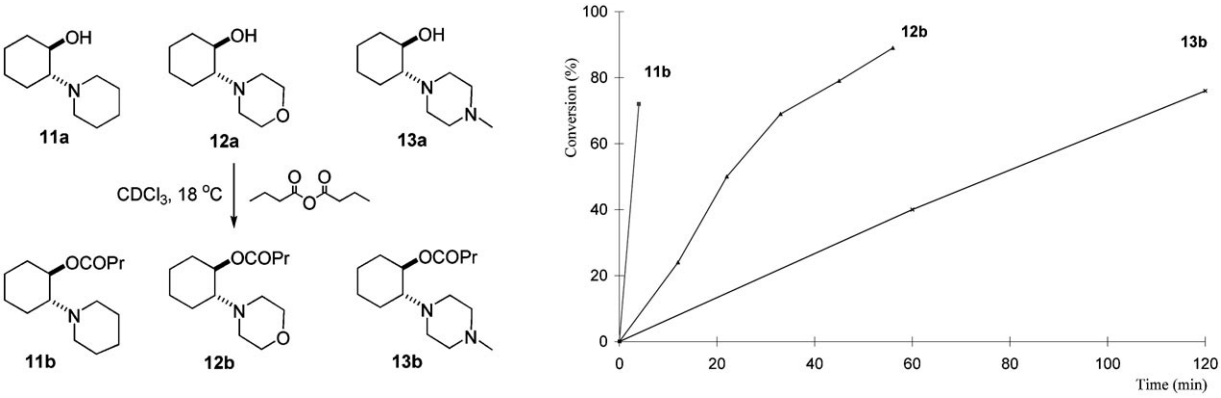


Figure 3. Acylation of amino alcohols influenced by electronic effects.

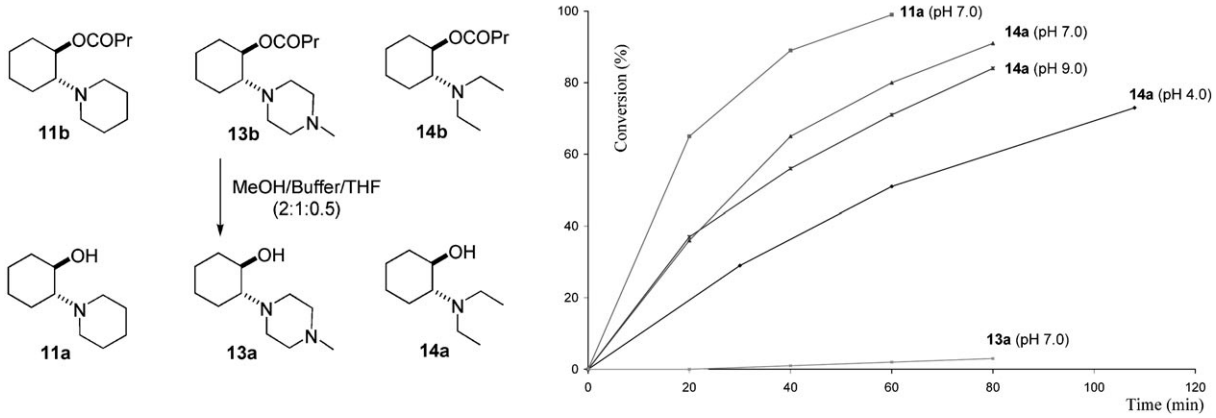
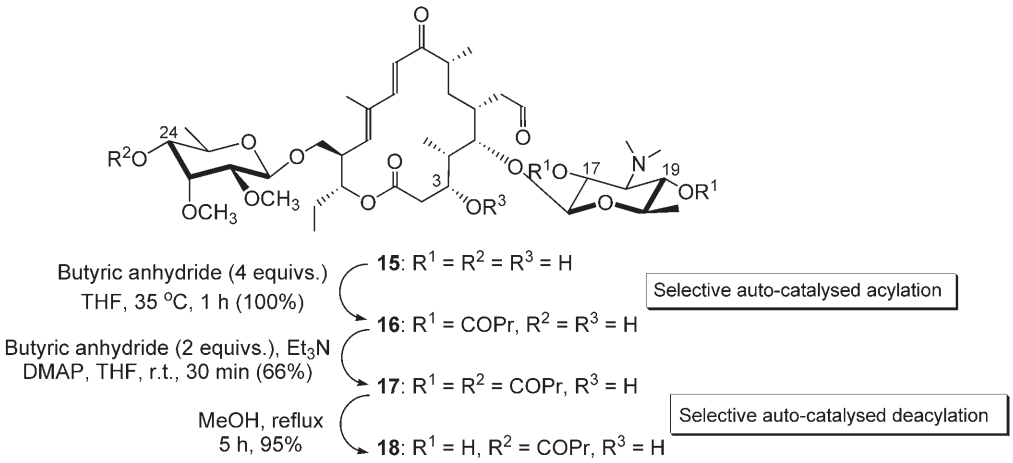


Figure 4. Methanolysis of amino esters (40 °C, THF/MeOH, buffer. Not shown: addition of 1 equivalent of TFA quenches the reaction altogether).

ester is not significantly catalysed by (external) base (Figure 4). However, the methanolysis was fully impeded in the presence of a stoichiometric amount of TFA.

Finally, thee methanolysis of **11b** and **13b** in buffer (pH 7.0, MeOH/buffer/THF = 2/1/0.5) was compared with that of ester **14b** (also shown in Figure 4). The slight rate enhancement seen with **11b** might be reasoned by steric effects: the more confined piperidine residue of **11b** imposes less hindrance than the diethylamine residue of **14b**. In contrast to this, the second nitrogen in **13b** inhibits methanolysis almost completely. This result again suggests that additional amino groups may act in competition with the original ones and inhibit the reaction, for example, by slowing protonation at the correct ester-proximal amino group.



Scheme 2.

The observed decrease in activity upon protonation, especially if quantitative, is a strong argument against a general acid catalysis, including activation of the carbonyl groups by the intramolecular ammonium. The lack of a significant pH-dependence – except for complete protonation – also does not support a general base mechanism. It might indicate that an internal nucleophilic activation is important, or/and a hydrogen bond-mediated proximity effect of the incoming nucleophile as proposed by Waddell et al.[7,9]

After the detailed investigations of the structure-reactivity relationship of amino alcohols and their esters, we turned to applications in synthesis. Amino alcohols are common functional groups occurring in many important compounds, including natural products. For instance, erythromycin[10] and desmycosin[11] are antibiotics possessing β-amino sugar moieties. Based on the high reactivity of amino alcohols, selective acylation/deacylation can be realised.[11,12] In the case of the more sensitive aldehyde desmycosin (**15**), its C-17 and C-19 hydroxy groups on the mycaminose sugar residue are adjacent to a dimethylamino group, hence they should have higher reactivity than C-3 and C-24-OH towards acylation. For a demonstration, **15** was treated with excess butyric anhydride (4 equivs.) in pure THF, and 17,19-*O*-dibutyryldesmycosin (**16**) was obtained as the only product. Further regioselective acylation on C-24-OH with Et_3N and DMAP afforded 17,19,24-*O*-tributyryldesmycosin (**17**). When heated in methanol, again only the C-17 and C-19-ester of **17** was methanolysed to give 24-*O*-butyryldesmycosin (**18**), the product selectively deprotected in proximity to the diethylamino group (Scheme 2).

Conclusions

Although the catalytic ability of amino alcohols as (trans-)acylation catalyst has been suggested and described in literature, the structures used were mainly restricted to β-amino alcohols. In our kinetic studies, a series of dialkylamino alcohols was acylated to explore spatial, steric, and electronic parameters to adjust acylation speed. The following factors have been found to decrease the acylation speed: a (carbon) spacer longer than four to five atoms, in a strained or rigid assembly that inhibits $OH \leftrightarrow NR_2$ proximity, bulky substituents on the amino group, or extra heteroatoms close to the amino group. Deacylation of amino esters follows similar lines, and in addition is not very dependent on the pH value (pH 4.0–9.0) of the solvent, revealing that this is a self-catalysed mechanism. Our results give clues on how to optimise the structure of amino alcohols to generate more effective organocatalysts. Through the selective acylation of desmycosin (**15**), we have also proven that the property of amino alcohols can be applied as a protection-deprotection strategy in organic synthesis. Since amino alcohols are common structural elements in natural products and drugs, the effects described here must be accounted for during synthetic planning, or even can be utilised to circumvent selectivity problems in total syntheses.

Experimental Section

Details of experimental conditions, instrumentation, and further examples can be found in the Supporting Information.

Chromatographic Analyses

Reversed phase HPLC analyses were performed with Merck RP 18, LiChrospher 100, 5 μm silica gel, 4×250 mm, 1 mL min^{-1}, at 51 bar. GC analyses were performed on a DB-5 MS column, 20 m×0.25 mm, film 0.25 μm, flow 0.8 mL min^{-1} He. GC conditions **A:** 0–4 min: 60 °C; 4–25 min: 60 °C→290 °C (10 °C min^{-1}); 26–29 min: 290 °C; pressure: 65 kPa. Conditions **B:** 0–6 min: 60 °C; 7–25 min:

60 °C→290 °C (12 °C min^{-1}); 26–30 min: 290 °C; pressure: 65 kPa. Conditions **C:** 0–6 min: 80 °C; 7–27 min: 60 °C→290 °C (11 °C min^{-1}); 28–30 min: 290 °C; pressure: 65 kPa.

General Procedure for the Preparation of *trans*-β-Aminocyclohexanols 11a–14a

To a solution of cyclohexene oxide (1.43 mL, 14.2 mmol) and dialkylamine (14.2 mmol) in 5 mL of dry CH_3CN, ground $Ca(OTf)_2$ (600 mg, 0.13 equiv.) was added. The reaction tube was sealed with a Teflon® cap. The solution was pre-stirred for 30 s, then was irradiated in the microwave (300 Watt, 70 °C) for 5 min. After the tube had been cooled to 50 °C by gas-jet cooling, the solvent turned red and homogeneous. After the CH_3CN had been evaporated, the residue was extracted with 200 mL of Et_2O and washed with saturated $NaHCO_3$ (3×10 mL), water (3×10 mL) and brine (1×10 mL). The solvent was dried over Na_2SO_4 and removed in vacuum to give the product. No further purification was needed.

***trans*-2-Piperidinylcyclohexanol (11a):** According to the general procedure, amino alcohol **11a** was obtained as a colourless oil; yield: 99%; R_f: 0.24 (petroleum ether:ethyl acetate:Et_3N = 2:1:0.01); GC (conditions B): 14.15 min; GC purity: >97%; ^{1}H NMR (399.9 MHz, $CDCl_3$, TMS): δ = 1.12–1.26 (m, 4H), 1.43–1.45 (m, 2H), 1.48–1.64 (m, 4H), 1.67–1.72 (m, 1H), 1.75–1.79 (m, 2H), 2.09–2.16 (m, 2H), 2.32 (m, 2H), 2.64–2.69 (m, 2H), 3.32–3.44 (m, 1H), 4.13 (bs, 1H); ESI-MS: *m/z* (%) = 184 (96%) $[M+H]^+$.

Kinetic Study and General Procedure for the Acylation of Amino Alcohols

An amino alcohol (0.23 mmol) and butyric anhydride (21 μL, 0.25 mmol) were dissolved with $CDCl_3$ (0.67 mL) in an NMR tube. The sample was scanned for ^{1}H NMR, monitoring the acylation process at 18 °C. When the test was finished, the sample was transferred to 100 mL of Et_2O. The solution was washed with $NaHCO_3$ (3×10 mL), H_2O (1×10 mL), and brine (1×10 mL), and was dried over Na_2SO_4. After the solvent had been evaporated under vacuum, the crude product was purified by flash chromatography to give the butyric ester.

***trans*-2-Piperidinylcyclohexyl butyrate (11b):** Ester **11b** was prepared from **11a** according to the general procedure, and purified by flash chromatography on silica (petroleum ether:ethyl acetate:Et_3N = 10:1:0.01) to afford a pale yellow oil; R_f: 0.65 (petroleum ether:acetone = 5:1); GC (conditions A): 15.60 min; GC purity: >99%; ^{1}H NMR (399.9 MHz, $CDCl_3$, TMS): δ = 0.98 (t, J = 7.4 Hz, 3H), 1.14–1.51 (m, 10H), 1.68 (sextet, J = 7.4 Hz, 2H), 1.63–1.1.75 (m, 2H), 1.82–1.85 (m, 1H), 1.93–1.98 (m, 1H), 2.28 (dt, J = 1.5 Hz, J = 7.4 Hz, 2H), 2.31–2.40 (m, 3H), 2.57–2.63 (m, 2H), 4.84–4.90 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, TMS): δ = 13.83, 18.65, 24.44, 24.68, 25.00, 25.13, 26.79, 32.06, 36.75, 50.22, 67.79, 71.61, 173.04; ESI-MS: *m/z* (%) = 254 (100) $[M+H]^+$, 276 (30) $[M+Na]^+$.

Kinetic Study of the Methanolysis of Amino Esters 11b, 13b, and 14b

The amino ester (0.23 mmol) was dissolved in a mixture of commercial pH buffer (4 mL), methanol (2 mL), and THF (1 mL). The solution was shaken on a LabMate Organic Synthesizer™ at 40 °C. In every given time interval (cf. Figure 4), 0.9 mL of the solution was taken out and diluted with 50 mL ethyl acetate. The organic layer was washed with H_2O (2×5 mL) and brine (1×5 mL), and was dried over Na_2SO_4. The solvent was completely removed under vacuum and the residue was submitted to ^{1}H NMR to determine the composition (conversion rate). There was no need to purify the resulting amino alcohols **11a**, **12a**, and **13a** after completion of the reaction.

29-*O*-Butyryldesmycosin (18)

A solution of **17** (15 mg, 16 μmol) in 5 mL of methanol was refluxed for 5 h. The solvent was removed under vacuum and the residue was purified by flash chromatography on silica gel (petroleum ether:acetone = 2 : 1) to give **18** as a colourless oil; yield: 13 mg (95%); R_f: 0.15 (petroleum ether:acetone:Et_3N = 50:50:1); RP-HPLC: 4.27 min (CH_3CN:H_2O:Et_3N = 90:10:0.01, column size: 4×250 mm, 5 μm); LC purity: 100%; ^{1}H NMR (399.9 MHz, $CDCl_3$, TMS): δ = 0.93 (t, J = 7.5 Hz, 3H), 0.97 (t, J = 7.5 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H), 1.20 (d, J = 6.7 Hz, 3H), 1.27 (d, J = 5.9 Hz, 3H), 1.44–1.52 (m, 2H), 1.56–1.66 (m, 1H), 1.68 (sextet, J = 7.5 Hz, 2H), 1.79 (d, J = 1.0 Hz, 3H), 1.84–1.88 (m, 1H), 1.85–1.91 (m, 1H), 1.94 (d, J = 16.6 Hz, 1H), 2.08–2.20 (m, 1H), 2.2.28–2.35 (m, 1H), 2.34 (t, J = 7.5 Hz, 2H), 2.39 (t, J = 10.7 Hz, 1H), 2.50 (t, J = 10.4 Hz, 1H), 2.52 (s, 6H), 2.51–2.54 (m, 1H), 2.92 (dd, J = 18.1 Hz, J = 9.6 Hz, 1H), 2.94–2.99 (m, 14H), 3.05 (dd, J = 8.0 Hz, J = 2.8 Hz, 1H), 3.06 (t, J = 9.6 Hz, 1H), 3.24–3.31 (m, 1H), 3.47 (dd, J = 10.9 Hz, J = 9.9 Hz, 1H), 3.48 (s, 3H), 3.52 (s, 3H), 3.56 (dd, J = 9.7 Hz, J = 6.5 Hz, 1H), 3.74 (d, J = 9.6 Hz, 1H), 3.84 (d, J = 10.5 Hz, 1H), 3.89 (t, J = 2.4 Hz, 1H), 3.91 (dd, J = 10.0 Hz, J = 6.1 Hz, 1H), 4.00 (dd, J = 9.7 Hz, J = 4.0 Hz, 1H), 4.26 (d, J = 7.1 Hz, 1H), 4.46 (dd, J = 10.0 Hz, J = 2.7 Hz, 1H), 4.63 (d, J = 8.1 Hz, 1H), 4.98 (td, J = 9.8 Hz, J = 2.5 Hz, 1H), 5.89 (d, J = 10.3 Hz, 1H), 6.26 (d, J = 15.7 Hz, 1H), 7.32 (d, J = 15.7 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ = 9.82, 10.38, 13.12, 13.75, 17.62, 17.49, 17.92, 18.53, 25.58, 29.56, 36.28, 39.41, 41.84, 41.92, 43.85, 44.73, 45.07, 59.59, 61.60, 67.40 (2×CH), 69.24, 70.56, 70.49, 70.79, 70.83, 73.29, 74.41, 75.20, 77.76, 80.58, 100.97 (2×CH), 118.62, 134.82, 141.89, 147.86, 172.59, 173.73, 202.57, 202.83; ESI-MS: *m/z* (%) = 842 (70) $[M+H]^+$, 874 (100) $[M+Na]^+$, 840 (100) $[M-H]^-$; HR-ESI-MS: *m/z* = 842.49050, calcd. for $C_{43}H_{72}O_{15}N$ $[M+H]^+$: 842.48965, 864.47158, calcd. for $C_{43}H_{71}O_{15}NNa$ $[M+Na]^+$: 864.47159.

Acknowledgements

We are grateful for a grant from the German Research Council (DFG We 1467/7–1).

References

[1] For recent selected examples and further references see: a) A. L. Braga, D. S. Lüdtke, F. Vargas, M. W.

Paixão, *Chem. Commun.* **2005**, 2512–2514; b) A. L. Braga, D. S. Lüdtke, P. H. Schneider, F. Vargas, A. Schneider, L. A. Wessjohann, M. W. Paixão, *Tetrahedron Lett.* **2005**, *46*, 7827–7830; c) A. L. Braga, R. M. Rubim, H. S. Schrekker, L. A. Wessjohann, M. W. G. de Bolster, G. Zeni, J. A. Sehnem, *Tetrahedron: Asymmetry* **2003**, *14*, 3291–3295; d) S.-L. Jeon, H.-M. Li, C. García, L. K. LaRochelle, P. J. Walsh, *J. Org. Chem.* **2005**, *70*, 448–455; e) J. Huang, J. C. Ianni, J. E. Antoline, R. P. Hsung, M. C. Kozlomsky, *Org. Lett.* **2006**, *8*, 1565–1568; f) I. Schiffers, T. Ratanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm, *J. Org. Chem.* **2006**, *71*, 2320–2331; g) A. L. Braga, M. W. Peixao, B. Westermann, P. H. Schneider, L. A. Wessjohann, *Synlett* **2007**, 917–920.

[2] a) M. M Werber, Y. Shalitin, *Bioorg. Chem.* **1973**, *2*, 202–209; b) M. N. Khan, *J. Org. Chem.* **1985**, *50*, 4851–4855; c) J. Hine, M. N. Khan, *J. Am. Chem. Soc.* **1977**, *99*, 3847–3848; d) R. A. Moss, R. C. Nahas, S. Ramaswami, *J. Am. Chem. Soc.* **1977**, *99*, 627–629; e) U. K. Tonellato, *J. Chem. Soc., Perkin Trans. 2* **1977**, 821–827.

[3] For lead references on DMAP and its derivatives see: a) W. Steglich, G. Höfle, *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem. Intel. Ed. Engl.* **1969**, *8*, 981; b) G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson, I. B. Campbell, *J. Org. Chem.* **2003**, *68*, 3844–3848; c) A. C. Spivey, D. P. Leese, F. Zhu, S. G. Davey, R. L. Jarvest, *Tetrahedron* **2004**, *60*, 4513–4525; d) E. P. Kündig, T. Lomberget, R. Gragg, C. Poulard, G. Bernardinelli, *Chem. Commun.* **2004**, 1548–1549; e) G. Fu, *Acc. Chem. Res.* **2004**, *37*, 542–547; f) J. A. MacKay, E. Vedejs, *J. Org. Chem.* **2004**, *69*, 6934–6937; g) S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem. Eur. J.* **2005**, *11*, 4751–4757; h) C. B. Fischer, S. Xu, H. Zipse, *Chem. Eur. J.* **2006**, *12*, 5779–5784.

[4] For references on amino alcohols acting similar to DMAP see: a) K. I. Skorey, V. Somayaji, R. S. Brown, *J. Am. Chem. Soc.* **1989**, *111*, 1445–1452; b) T. Sammakia, T. B. Hurley, *J. Org. Chem.* **1999**, *64*, 4652–4664; c) T. Sammakia, T. B. Hurley, *J. Org. Chem.* **2000**, *65*, 974–978; d) K. A. Wayman, T. Sammakia, *Org. Lett.* **2003**, *5*, 4105–4108; e) G. T. Notte, T. Sammakia, P. J. Steel, *J. Am. Chem. Soc.* **2005**, *127*, 13502–13503; f) G. T. Notte, T. Sammakia, *J. Am. Chem. Soc.* **2006**, *128*, 4230–4231.

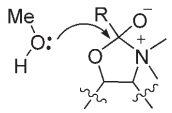
[5] a) D. M. Blow, *Acc. Chem. Res.* **1976**, *9*, 145; b) L. Hedstrom, *Chem. Rev.* **2002**, *102*, 4501–4523; c) L. A. Wessjohann, D. G. Rivera, F. Coll, *J. Org. Chem.* **2006**, *71*, 7521–7526.

[6] a) H. M. R. Hoffmann, O. Schrake, *Tetrahedron: Asymmetry* **1998**, *9*, 1051–1057; b) O. Schrake, M. H. Franz, R. Wartchow, H. M. R. Hoffmann, *Tetrahedron* **2000**, *56*, 4453–4465.

[7] T. G. Waddell, T. Rambalakos, K. R. Christie, *J. Org. Chem.* **1990**, *55*, 4765–4767.

[8] See Supporting Information. Butyrates were used because the reactions rates are in a convenient time scale for both acylation and deacylation.

[9] Stabilisation of the tetrahedral transition state during acyl transfer could also play a relevant role, compared to general base (or ammonium acid) catalysis.



[10] A. J. Bryskier, J. P. Butzler; H. C. Neu, P. M. Tulkens, in: *Macrolides: Chemistry, Pharmacology and Clinical Uses*, Arnette Blackwell, Paris, **1993**.

[11] S. Mutak, N. Maršić, M. D. Kramarić, D. Pavlović, *J. Med. Chem.* **2004**, *47*, 411–431.

[12] M. J. Acland, P. J. Atkins, N. B. Jones, *J. Chem. Res. (S)* **1991**, 142–142; *J. Chem. Res. (M)* **1991**, 1265–1278.

