Tetrahedron: *Asymmetry* 19 (2008) 2045–2050

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Substrate control by means of the chiral cavity of prolinamide derivatives of cholic acid in the organocatalyzed Michael addition of cyclohexanone to nitroolefins

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ARTICLE INFO

Article history:
Received 27 June 2008
Accepted 19 August 2008

ABSTRACT

Different prolinamide and bis-prolinamide derivatives were checked as organocatalysts in the asymmetric Michael addition of cyclohexanone to aromatic nitroolefins, and the derivative bearing a D-prolinamide moiety linked at the 7-position emerged as the most efficient, giving the Michael adducts in satisfactory yield and ees of up to 95%. The corresponding system having a free OH group at the 3-position of the cholestanic backbone afforded the opposite enantiomer of the product, suggesting that the transition state is developed at the inner part of the cholestanic cavity, which is responsible for the substrate control determining the stereochemical outcome of the reaction.

1. Introduction

The asymmetric Michael addition of carbon nucleophiles to nitroolefins has attracted a lot of attention because it allows functionalized products with multiple stereogenic centres to be obtained in a single step.[1] Its organocatalyzed version, pioneered by List[2a] and Barbas,[2b] represents a satisfactory answer to the demand for environmentally friendly reaction conditions leading to enantiomerically enriched products.[3] Excellent results have been obtained in the Michael addition of carbonyl compounds to nitroalkenes using chiral amines as organocatalysts,[4] which promote the reaction via an enamine pathway.[5] Among these, proline derivatives bearing substrate orienting functional groups[6] succeeded in reaching good levels of asymmetric induction. An alternative approach to the attainment of high diastereoisomeric and enantiomeric excesses by means of substrate control can be realized by using a proline derivative where the aminoacid moiety is a part of a chiral cavity in which the reaction takes place. Following this idea, we synthesized prolinamide derivatives of bile acids by linking a proline moiety to the different functionalized positions of cholic and deoxycholic acids, which were successfully used as organocatalysts in the direct asymmetric aldol reaction.[7] The effectiveness of these systems relies on the cholestanic structure that forms a functionalized chiral cavity with the appended prolinamide groups that were able to exert a good stereochemical control on the orientation of the substrate.[7] Furthermore, both position on the cholestanic backbone and absolute configuration of the proline moiety, as well as the presence of free hydroxyl groups, play a significant role in determining the stereochemical outcome of the reaction.[7] Since the amine catalyzed Michael addition of ketones to nitroolefins proceeds via an enamine intermediate, as in the proline-promoted aldol reaction, we reasoned that this class of organocatalysts could also succeed in this reaction. To verify this hypothesis, the prolinamide and bis-prolinamide derivatives of cholic acid reported in Figure 1 were checked as organocatalysts in the asymmetric Michael addition of cyclohexanone to aromatic nitroolefins.

These derivatives possess D- or L-prolinamide moieties linked to the stereochemically demanding 7 and 12 positions of the cholic acid and free or protected hydroxyl groups, to check the effect of these structural features on the outcome of the reaction.

2. Results and discussion

2.1. Synthesis of the organocatalysts

The synthesis of the bis-prolinamide derivatives **3** was performed starting from the 7,12-dioxime derivative of cholic acid as outlined in Scheme 1. Compound **5** was obtained from cholic acid in three steps in 85% overall yield, as previously described in the literature,[8] and was eventually reduced, with complete stereoselectivity, to the 7,12-diamino derivative **6** by means of catalytic hydrogenation, followed by reaction with Zn in acetic acid. The prolinamide derivatives **7** were obtained by reacting the diamine **6** with D-Boc-Proline in the presence of isobutylchloroformate at

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doi:10.1016/j.tetasy.2008.08.018

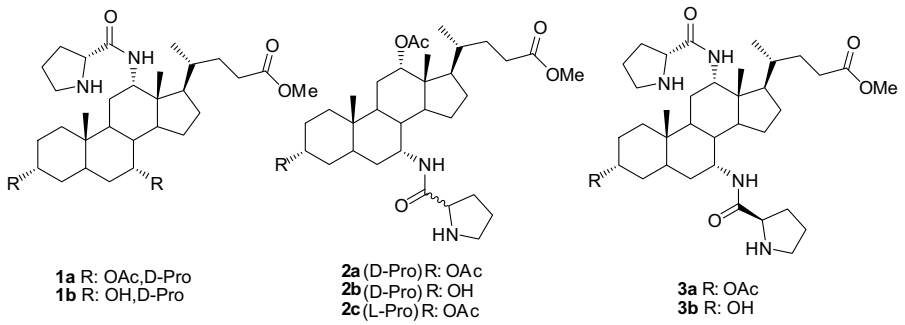
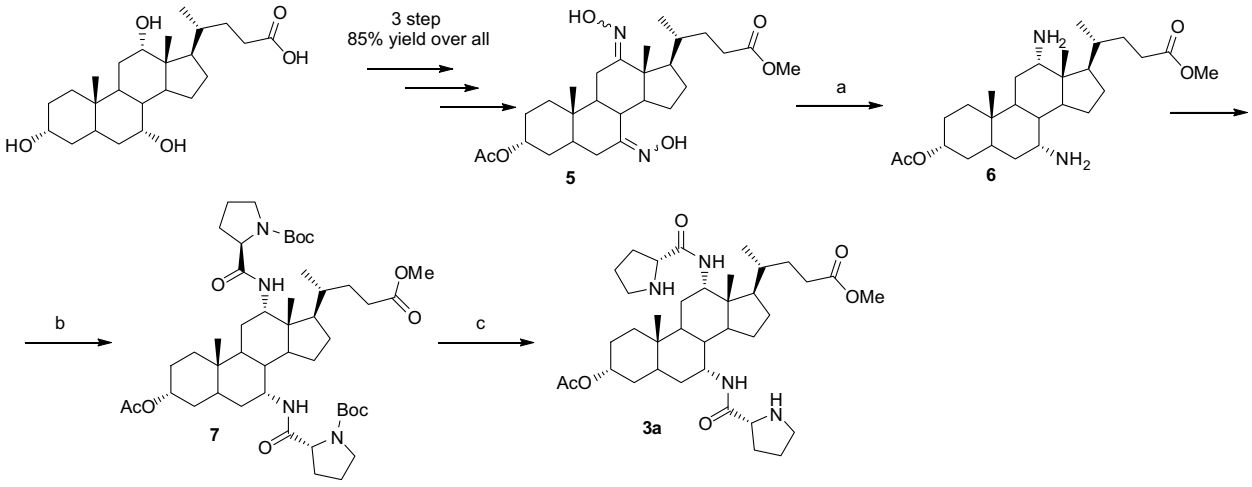


Figure 1. Structure of bile acid derived organocatalysts.

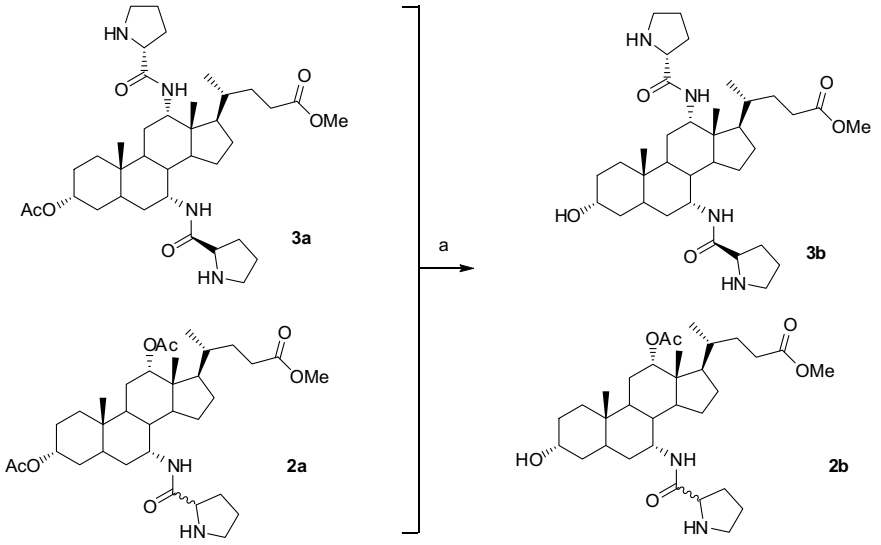


Scheme 1. Synthesis of bis-prolinamide bile acid derivative **3a**. Reagents and conditions: (a) $PtO_2{\cdot}xH_2O$, AcOH, H_2 (2 bar), rt, 6 d, then Zn powder, rt, 12 h; (b) D-Boc-Pro, isobutylchloroformate, NMM, CH_2Cl_2, 0 °C to rt, 26 h; (c) CH_2Cl_2, TFA, rt 15 min.

room temperature[7] in 50% yield after chromatographic purification. Organocatalyst **3a** was obtained in quantitative yield by removing the Boc protecting group by means of trifluoroacetic acid in dichloromethane solution. Products **2b** and **3b** were prepared by hydrolysis of the corresponding 3-acetate derivatives with HCl in methanol (Scheme 2).

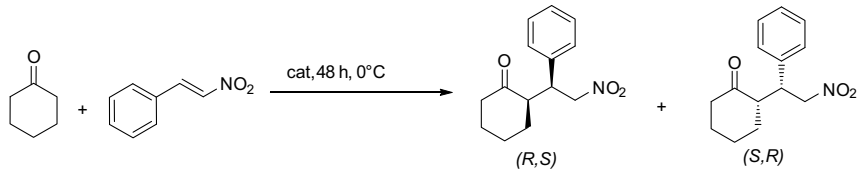
2.2. Michael addition of cyclohexanone to nitroolefins

Derivatives **1**–**3** were assayed as organocatalysts in the asymmetric Michael addition of cyclohexanone to β-nitrostirene, and the results obtained are reported in Table 1. The reactions were performed by stirring cyclohexanone and the organocatalyst in



Scheme 2. Synthesis of **3b** and **2b**. Reagents and conditions: (a) concd HCl., MeOH, 24 h, rt.

Table 1
Michael addition of cyclohexanone to *trans*-β-nitrostyrene in the presence of organocatalysts **1–3**



Entry[a]	Cat.	Cat. loading (mol %)	Solvent	ee[b] (%)	A.C.[c]	Conv.[d] (%)
1	**1**[a]	10	DCM	41	(*R*,*S*)	44
2	**2a**	10	DCM	61	(*R*,*S*)	94
3	**2**[a]	5	DCM	62	(*R*,*S*)	38
4	**2a**	10	PhMe	70	(*R*,*S*)	80
5	**2a**	5	PhMe	79	(*R*,*S*)	28
6	**2a**	10[e]	PhMe	82	(*R*,*S*)	50
7	**2a**	10	*i*-PrOH	23	(*R*,*S*)	8
8	**2c**	10	DCM	34	(*S*,*R*)	65
9	**2b**	10	DCM	60	(*S*,*R*)	50
10	**2b**	10	PhMe	75	(*S*,*R*)	36
11	**1b**	10	DCM	47	(*S*,*R*)	68
12	**3a**	5	DCM	56	(*R*,*S*)	97
13	**3a**	5	PhMe	50	(*R*,*S*)	75
14	**3a**	5	THF	10	(*R*,*S*)	31
15	**3b**	5	DCM	65	(*S*,*R*)	53
16	**3a**	5	EtOH	27	(*S*,*R*)	47
17	**3a**	5	*i*-PrOH	36	(*S*,*R*)	19

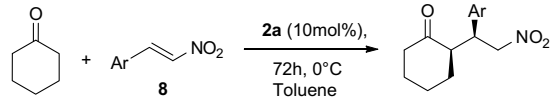
[a] Reaction conditions: cyclohexanone (2 equiv), *trans*-β-nitrostyrene (1 equiv), organocatalyst, solvent (1 mL), 48 h, rt.
[b] Enantiomeric excess of the *syn* diastereoisomer (de >98%, evaluated by ^{1}H NMR) was determined by enantioselective HPLC: Chiralcel OJ, Hexane/2-propanol 97:3, 220 nm, 1 mL/min.
[c] Absolute configuration of the prevailing enantiomer was determined by comparison with the literature data.
[d] Determined by ^{1}H NMR.
[e] Reaction was performed at 0 °C for 60 h.

the solvent, then adding β-nitrostirene after 1 h, and were interrupted usually after 48 h.

All the reactions proceeded with complete diastereoselectivity in favour of the *syn*-diastereoisomer. Derivative **1a**, bearing a D-prolinamide moiety linked to the 12-position, afforded, in dichloromethane at room temperature, the reaction product in 44% yield and 41% ee (entry 1). Better results were obtained using **2a**, which possesses the same moiety linked at 7-position: under the same reaction conditions, the Michael adduct was obtained in 94% yield and 61% ee (entry 2). Lowering the catalyst loading gave rise to a lower yield, without affecting the extent of asymmetric induction (entry 3). The use of toluene as a reaction solvent gave a higher ee (entry 4) that further increased when using lower catalyst loading (entry 5) that, unfortunately, afforded a lower yield of the product. On lowering the temperature, the extent of asymmetric induction increased, and the product was obtained in 50% yield and 82% ee (entry 6). The use of the protic solvent 2-propanol gave poor results in terms of both yield and ee (entry 7). Derivative **2c**, bearing a L-prolinamide moiety at the same position as **2a**, gave worse results with respect to its diastereoisomer in terms of both yield and ee (entry 8), suggesting that D-prolinamide moiety is in a matched relationship with the cholestanic backbone when linked at the 7-position. The absolute configuration of the prevailing enantiomer of the product depends on the absolute configuration of the prolinamide moiety: as a matter of fact the same prevailing enantiomer was obtained using **1a** and **2a**, whereas the sense of asymmetric induction is inverted when the reaction was promoted by **2c**. It is noteworthy that the same stereoselectivity inversion is observed using **2b** (entry 9), which possesses a D-prolinamide moiety linked at the 7-position, as **2a**, but has a free hydroxyl group at the 3-position. In addition, this organocatalyst gave better results in terms of asymmetric induction with respect to **2c**, which further improved using toluene as a solvent (entry 10). These results suggest that the free OH on the cholestanic backbone enters the transition state leading to the product, changing the asymmetric induction mechanism. It is conceivable that this could happen only if the transition state is developed at the inner part of the chiral cavity, formed by the cholestanic backbone and the appended prolinamide moiety, where the 3-OH group is directed. The change of the asymmetric induction mechanism depending on the presence of a free 3-OH group is also observed using **1b**, which possesses a D-prolinamide moiety linked at the 12-position (entry 11), which gave the opposite prevailing enantiomer with respect to **1a** (entries 1 and 11). These results point out the role of the chiral cavity of these organocatalysts in determining the stereochemical outcome of the Michael reaction independently of the position of the prolinamide moiety on the cholestanic backbone. Since **2a** gave the best results in terms of both yield and ee of the product and gave the same prevailing enantiomer as **1a**, we were interested in checking if two D-prolinamide moieties linked at the 7- and 12-positions could work in a synergistic manner, affording higher asymmetric induction. The bis-prolinamide derivative **3a** gave the reaction product in quantitative yield under a 5% catalyst loading and in a slightly lower ee than that obtained using **2a** (entry 12). The higher reaction rate and the very similar asymmetric induction extent suggest that the two D-prolinamide moieties of **3a** work independently as organocatalysts of the reaction. No better results were obtained by changing reaction solvent (entries 13 and 14). The sense of asymmetric induction still changes in passing from **3a** to **3b**, the analogues possessing a free OH group at the 3-position (entry 15), and a slight improvement of the ee is also observed. The same enantioselectivity inversion is observed when polar protic solvents, such as ethanol or 2-propanol, were used (entries 16 and 17): however, the poor results in terms of both yield and ee make these reaction conditions scarcely interesting.

The conditions giving the best results in the asymmetric Michael addition of cyclohexanone and β-nitrostirene, that is, 10% of **2a** as an organocatalyst in toluene at 0 °C, were used to test the reaction with other aromatic nitroolefins, and the results are reported in Table 2.

Table 2
Michael addition of cyclohexanone to aromatic nitroolefins **8** in the presence of organocatalyst **2a**



8a Ar:*p*-$NO_2C_6H_4$ **8e** Ar:2-furyl
8b Ar:*p*-$MeOC_6H_4$ **8f** Ar:*p*-MeC_6H_4
8c Ar:*o*-$NO_2C_6H_4$ **8g** Ar:2-naphthyl
8d Ar:*p*-BrC_6H_4 **8h** Ar:1,3-benzodioxoane-5-yl

Entry[a]	Ar	de[b] (%)	Conv.[b] (%)	ee[c] (%)
1	**8a**	98	64	93[d]
2	**8b**	98	55	55[e]
3	**8c**	98	59	49[f]
4	**8d**	62	65	80[g]
5	**8e**	61	68	82[h]
6	**8f**	70	66	79[i]
7	**8g**	71	65	75[j]
8	**8h**	98	26	95[k]

[a] Reaction conditions: cyclohexanone (2 equiv), nitroolefin (1 equiv), organocatalyst (10 mol %) and toluene, 0 °C, 72 h.
[b] Determined by ^{1}H NMR.
[c] Enantiomeric excess of the *syn* prevailing diastereoisomer was determined by enantioselective HPLC.
[d] Chiralcel OJ, 238 nm, 1 mL/min, Isoct/Ipa 80:20.
[e] Chiralpack AD, 238 nm, 1 mL/min, Hex/Ipa 95:5.
[f] Chiralpack AD, 254 nm, 0.5 mL/min, Hex/Ipa 90:10.
[g] Chiralpack AS, 238 nm, 1 mL/min, Hex/Ipa 90:10.
[h] Chiralpack AD, 254,nm, 0.7 mL/min, Hex/Ipa 90:10.
[i] Chiralcel OJ, 220 nm, 1 mL/min, Hex/Ipa 97:3.
[j] Chiralpack AS, 254 nm, 0.7 mL/min, Hex/Ipa 55:45.
[k] Chiralpack AS, 214 nm, 1 mL/min, Hex/Ipa 97:3.

All the reactions were stopped after 72 h for comparative purposes. Conversions ranging from 55% to 68% were obtained, with the only exception of substrate **8h** which gave a poor yield of the Michael adduct (entry 8), probably because the presence of an electron rich aromatic ring slows down the addition to a greater extent. The reaction is diastereoselective in favour of the *syn* diastereoisomer with all the substrates, but the extent depends on the nature of the nitroolefin. A general trend depending on the electronic character or the substitution pattern of the aromatic ring cannot be found: as a matter of fact, complete diastereoselectivity was obtained with both electron-poor and electron-rich substrates (entries 1 and 2) or with substrates bearing substituents on different positions of the aromatic ring (entries 1, 3 and 8). The same considerations can be made with regard to the substrates giving lower diastereoisomeric excesses (entries 4–7). The ees are moderate only for substrates **8b** and **8c** (entries 2 and 3). The other nitroolefins gave the Michael adducts with ees ranging from 75% to 95%. Again, a trend depending on electronic characteristics or substitution of the aromatic rings cannot be found, and there is no correlation between diastereoselectivity and enantioselectivity. In fact, starting from olefin **8b** a Michael adduct with high diastereoisomeric excess but moderate ee was obtained (entry 2), whereas substrate **8e** afforded a product with moderate diastereoselectivity and good ee (entry 5).

3. Conclusion

Screening of different prolinamide and bis-prolinamide derivatives of cholic acid as organocatalysts in the asymmetric Michael addition of cyclohexanone not only allowed us to find a chiral system that is able to afford satisfactory yields of the products and ees up to 95%, but also pointed out the role of the chiral cavity constituted by the cholestanic backbone and the appended prolinamide moieties in determining the stereochemical outcome of the reaction. As a matter of fact, the presence of a free hydroxyl group, which can interact with the substrate only in a transition state developed at the inner part of the cavity, gives rise to the change of the sense of asymmetric induction, with respect to the corresponding systems having a protected hydroxyl group. This result also has a practical implication given that deprotection of the OH group is easily realized, so that it is possible to obtain both enantiomers of the Michael adducts starting from the same chiral architecture.

4. Experimental

4.1. General procedures and materials

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-300 300 MHz NMR spectrometer, using TMS as external standard. The following abbreviations are used: s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet and br = broad. HPLC analyses were performed on a JASCO PU-980 intelligent HPLC pump equipped with a JASCO UV-975 detector. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. Melting points were taken using a Kopfler Reichert-Jung apparatus, and are uncorrect. IR spectra were recorded on a Perkin-Elmer 1710 spectrophotometer.

TLC analyses were performed on silica gel 60 sheets; flash chromatography separations were carried out on columns using silica gel 60 (230–400 mesh). Toluene was refluxed over sodium and distilled before use. THF was refluxed over Na/K alloy and distilled before use. CH_2Cl_2 and *N*-methylmorpholine were refluxed over CaH_2 and distilled before use. Zn powder was washed with concentrated HCl, water, acetone and diethylether before use. Glacial acetic acid was used. Unless otherwise specified, the reagents were used without any purification. Methyl 3α-acetyloxy-12α,7α-dioxime-5β-cholan-24-oate **5**,[8] methyl 3α,7α-diacetyloxy-12α-(D-prolinoyl)amino-5β-cholan-24-oate **1a**,[7b] methyl 3α,7α-dihydroxy-12α-(D-prolinoyl)amino-5β-cholan-24-oate **1b**,[7b] methyl 3α,12α-diacetyloxy-7α-(D-prolinoyl)amino-5β-cholan-24-oate **2a**,[7b] and methyl 3α,12α-diacetyloxy-7α-(L-prolinoyl)amino-5β-cholan-24-oate **2c**[7b] were obtained as previously described, and matched the reported characteristics.

4.2. Synthesis of organocatalysts

4.2.1. Methyl 3α-acetyloxy-12α,7α-diamino-5β-cholan-24-oate 6

Hydrated PtO_2 (120 mg, 12,5 mol %) was added to a solution of dioxime **5** (2.07 g, 4.22 mmol) in glacial acetic acid (9 mL), and the mixture was stirred under H_2 (2 bar) at room temperature for six days. The solid was filtered off and powdered Zn (4.5 g, 33.72 mmol) was added to the solution, concentrated under vacuum to 2 mL. The mixture was stirred at room temperature for 12 h, then the solid was filtered off and washed with acetic acid. After concentration under reduced pressure, water was added and the aqueous solution was made basic with KOH pellets. The organic product was extracted with ethyl acetate and the organic extracts were dried (Na_2SO_4). The solvent was evaporated under vacuum affording pure amine. Yield 1.11 g, 57%. Mp 94–95 °C. $[\alpha]_D^{22} = +35.0$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0,73 (s, 3H, CH_3), 0,92 (s, 3H, CH_3), 0,97 (d, 3H, 21-CH_3), 1,00–2,60 (m, 28H, steroidal CH and CH_2), 2.01 (s, 3H, CH_3CO), 3.10 (br t, 1H, 12-CH), 3.16 (br t, 1H, 7-CH), 3.67 (s, 3H, OMe), 4.56 (m, 1H, 3-CH). ^{13}C NMR (40 MHz, $CDCl_3$, δ): 13.68, 17.31, 21.56, 22.81, 23.67, 26.03, 26.83, 27.72, 28.36, 31.01, 31.21, 34.76, 35.06, 35.13, 35.26, 36.05, 39.66, 41.72, 41.99, 46.23, 47.67, 47.90,

51.61, 54.03, 74.47, 170.89 (acetate C=O), 174.63 (24 C=O). IR (KBr, cm^{-1}): 2961, 1735, 1654, 1636, 1560, 1458, 1382, 1261, 1164, 1096, 1033, 804. Anal. Calcd for $C_{27}H_{46}N_2O_4$: C, 70.09; H, 10.02; N, 6.05; O, 13.83. Found: C, 70.13; H, 10.01; N, 6.04.

4.2.2. Methyl 3α-acetyloxy-7α,12α-bis(D-Boc-Prolinoyl)amino-5β-cholan-24-oate 7

To a solution of N-Boc protected D-proline (512 mg, 2.38 mmol) in anhydrous CH_2Cl_2, *N*-methylmorpholine (290 μL, 2.63 mmol) was added and the mixture was cooled to −20 °C, then isobutylchloroformate (340 μL, 2.38 mmol) was added. The reaction temperature was maintained at −20 °C for 5 min, then a CH_2Cl_2 solution of diamine **6** (500 mg, 1.08 mmol) was added dropwise over 15 min at 0 °C. The reaction mixture was stirred for 26 h. Finally the reaction mixture was treated with HCl acq. and $NaHCO_3$ acq. and NaCl acq. then dried over Na_2SO_4. The organic phases were concentrated in vacuo, and the residue was purified by column chromatography on silica gel (AcOEt/Hex 1:1) affording the pure product. Yield 500 mg, 54%. Mp 66–67 °C. $[\alpha]_D^{22} = +79.5$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0,77 (s, 3H, CH_3), 0.90 (d, 3H, 21-CH_3), 0.94 (s, 3H, CH_3), 1.00–2.40 (m, 28H, steroidal CH and CH_2 and 8H 3′ and 4′-CH_2 of Boc-Pro), 1.46 (s, 18H, Boc 6CH_3) 2.03 (s, 3H, CH_3CO), 3.35 (br m, 1H, 2′-CH of 7-Boc-Pro), 3.37 (br m, 4H, 3′-CH_2 of 7 and 12-Boc-Pro) 3.66 (s, 3H, OMe), 4.01 (br m, 1H, 2′-CH of 12-Boc-Pro), 4.27 (br d, 1H, 12-CH), 4.37 (br d, 1H, 7-CH), 4.56 (m, 1H, 3-CH), 7.60 (br d, 1H, 7 and 12-NH amide). ^{13}C NMR (40 MHz, $CDCl_3$, δ): 13.65, 14.29, 16.99, 21.65, 23.15, 23.44, 24.51, 24.74, 26.92, 27.09, 27.39, 28.56 (3C, Boc), 28.63 (3C, Boc), 29.43, 30.98, 31.43, 31.92, 34.84, 35.01, 35.54, 37.10, 41.53, 44.79, 45.03, 46.07, 47.16, 47.31, 48.41, 51.51, 51.87, 59.91, 60.25, 60.48, 74.62, 79.85, 80.38, 170.44 (acetate C=O), 171.03 (7 and 12 Boc C=O), 171.50 (7 and 12 amide C=O), 174.58 (24 C=O). IR (KBr, cm^{-1}): 2962, 2874, 1739, 1679, 1528, 1401, 1365, 1260, 1164, 1120, 1088, 1026, 802. Anal. Calcd for $C_{47}H_{76}N_4O_{10}$: C, 65.86; H, 8.94; N, 6.54; O, 18.67. Found: C, 65.88; H, 8.93; N, 6.55.

4.2.3. Methyl 3α-acetyloxy-12α,7α-bis(D-prolinoyl)amino-5β-cholan-24-oate 8

A solution of amide in CH_2Cl_2 (5 mL) was reacted with a large excess of TFA (5 mL) and stirred at rt for 30 min. The resulted mixture was washed with $NaHCO_3$ 5% to remove the excess of acid and extracted with CH_2Cl_2 (typically 3 × 30 mL). Organic phase was then washed with brine (3 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum affording chemical pure product. Yield 435 mg, quantitative. Mp 102–103 °C. $[\alpha]_D^{22} = +43.4$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.82 (s, 3H, CH_3), 0.84 (d, 3H, 21-CH_3), 0.96 (s, 3H, CH_3), 1.00–2.60 (m, 28H, steroidal CH and CH_2 and 8H 3′ and 4′-CH_2 of Pro), 1.99 (s, 3H, CH_3CO), 2.99 (br m, 1H, 2′-CH of 7-Pro), 3.09 (br m, 4H, 3′-CH_2 of 7 and 12-Pro) 3.66 (s, 3H, OMe), 3.78 (br m, 1H, 2′-CH of 12-Pro), 3.88 (br d, 1H, 12-CH), 4.24 (br d, 1H, 7-CH), 4.55 (m, 1H, 3-CH), 8.18 (br d, 1H, 7 and 12-NH amide). ^{13}C NMR (40 MHz, $CDCl_3$, δ): 13.61, 17.48, 21.42, 23.09, 23.22, 26.25, 26.49, 26.99, 27.43, 29.25, 30.73, 30.86, 31.05, 31.79, 34.68, 34.94, 35.83, 37.05, 41.25, 44.57, 45.29, 45.57, 47.35, 47.68, 48.89, 51.04, 51.64, 60.77, 61.13, 74.07, 170.34 (acetate C=O), 173.58 (7 and 12 amide C=O), 174.68 (24 C=O). IR (KBr, cm^{-1}): 2961, 2871, 1735, 1654, 1648, 1560, 1541, 1508, 1458, 1448, 1381, 1364, 1260, 1170, 1098, 1025, 801. Anal. Calcd for $C_{37}H_{60}N_4O_6$: C, 67.65; H, 9.21; N, 8.53; O, 14.61. Found: C, 67.66; H, 9.20; N, 8.55.

4.3. General procedure for 3-hydroxyl deprotection

A solution of the organocatalysts (1 equiv) in MeOH (typically 8 mL) was reacted with a large excess of concentrated HCl (typically 0.2 mL) and stirred at rt for 24 h. A 5% solution of $NaHCO_3$ was added to remove the excess of acid, and the product was extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was then washed with brine (3 × 50 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum affording chemical pure product.

4.3.1. Methyl 3α-hydroxy-12α,7α-bis(d-prolinoyl)amino-5β-cholan-24-oate 3b

Yield 90 mg, quantitative. Mp 133–135 °C. $[\alpha]_D^{22} = +112.7$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0,79 (s, 3H, CH_3), 0,85 (d, 3H, 21-CH_3), 0.92 (s, 3H, CH_3), 1.00–2.40 (m, 28H, steroidal CH e CH_2 and 8H 3′ and 4′-CH_2 of Pro), 3.03 (br m, 1H, 2′-CH of 7-Pro), 3.46 (br m, 4H, 3′-CH_2 of 7 and 12-Pro) 3.63 (s, 3H, OMe), 3.82 (br m, 1H, 2′-CH of 12-Pro), 3.85 (br d, 1H, 12-CH), 4.22 (br d, 1H, 7-CH), 4.36 (br d, 1H, 3-CH), 8.08 (br d, 1H, NH amide) 8.28 (br d, 1H, NH amide). ^{13}C NMR (40 MHz, $CDCl_3$, δ): 13.60, 17.75, 22.72, 23.08, 23.22, 26.56, 25.02, 26.17, 26.44, 26.87, 27.47, 29.45, 29.90, 30.57, 31.20, 31.70, 32.13, 34.76, 35.13, 35.96, 36.88, 37.09, 38.65, 39.88, 41.68, 41.94, 44.82, 45.47, 46.09, 46.82, 47.40, 47.75, 51.34, 51.69, 59.80, 60.81, 61.29, 61.99, 70.52, 71.81, 72.54, 172,54 (amide C=O), 173.55 (amide C=O), 174.83 (24 C=O). IR (KBr, cm^{-1}): 2937, 2862, 1737, 1669, 1538, 1458, 1433, 1371, 1340, 1309, 1247, 1197, 1167, 1089, 1068, 1012, 919, 820. Anal. Calcd for $C_{35}H_{58}N_4O_5$: C, 68.37; H, 9.51; N, 9.11 O, 13.01. Found: C, 68.38; H, 9.52; N, 9.09.

4.3.2. Methyl 3α-hydroxy-12α-acetyloxy-7α-(D-prolinoyl)-amino-5β-cholan-24-oate 2b

Yield 92 mg, quantitative. Mp 92–93 °C. $[\alpha]_D^{22} = +132.6$ (*c* 1.00, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 0.76 (s, 3H, CH_3), 0.84 (d, 3H, 21-CH_3), 0.96 (s, 3H, CH_3), 0.90–2.40 (m, 28H, steroidal CH and CH_2), 2.14 (s, 3H, 12-CH_3CO), 3.04 (br m, 2H, 3′-CH_2 of 7-Pro), 3.49 (br s, 1H, 7-CH), 3.67 (s, 3H, CH_3OCO), 3.77 (br s, 1H, 2′-CH of Boc-Pro), 5.13 (br s, 1H, 12-CH) 3.99 (m, 1H, 3-CH), 8.20 ppm (br s, NH amide). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 12.39, 17.61, 21.58, 22.74, 22.99, 25.79, 26.98, 27.24, 28.58, 29.30, 30.81, 31.02, 34.63, 34.79, 36.63, 41.35, 43.90, 45.32, 46.60, 47.35, 47.61, 51.61, 74.20, 75.40, 80.42, 170.37, 170.70, 171.18, 174.60, 198.11 ppm. IR (KBr, cm^{-1}): 2960, 2871, 1738 (br C=O), 1703 (C=O), 1679, 1654, 1526, 1506, 1457, 1437, 1398, 1368, 1245, 1162, 1118, 1083, 1022, 960, 887. Anal. Calcd for $C_{32}H_{52}N_2O_6$: C, 68.54; H, 9.35; N, 5.00 O, 17.12. Found: C, 68.56; H, 9.34; N, 5.00.

4.4. General procedure for the Michael reaction

The organocatalyst (5 or 10 mol %) was stirred in the solvent with cyclohexanone (0.5 mmol) for 1 h. *trans*-β-Nitrostyrene (0.25 mmol) was added and the mixture was stirred at the desired temperature, monitoring the reaction by TLC (SiO_2 ethyl acetate/hexane 30:70). The reaction was stopped by evaporating the solvent, and the crude product was analyzed by HPLC on a chiral stationary phase and ^{1}H NMR (see Tables).

Acknowledgements

The work was supported by the University of Pisa and Scuola Normale Superiore of Pisa.

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