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Stereoselective total synthesis of amicoumacin C

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ABSTRACT

The enantio- and diastereoselective total synthesis of amicoumacin C was achieved from L-phenylalanine in 17% overall yield through 13 steps via condensation between an amine and an acid segment. The amine segment was prepared from L-leucine in 42% yield by a 7-step sequence involving a diastereoselective reduction of an α-dibenzylamino ketone intermediate, while the acid segment was obtained from L-phenylalanine by using acidic hydrolysis of an acetonide-protected amide accompanied by concomitant lactonization as a key step.

1. Introduction

Amicoumacin C (**1**), an antibacterial substance first isolated from the culture broth of *Bacillus pumilus* BN-103 and later from *B. subtilis* 3 (probiotic strain),[1,2] belongs to a family of natural products characterized by a dihydroisocoumarin ring system linked, via an amide bond, to an unusual amino acid in most cases (Fig. 1).[3]

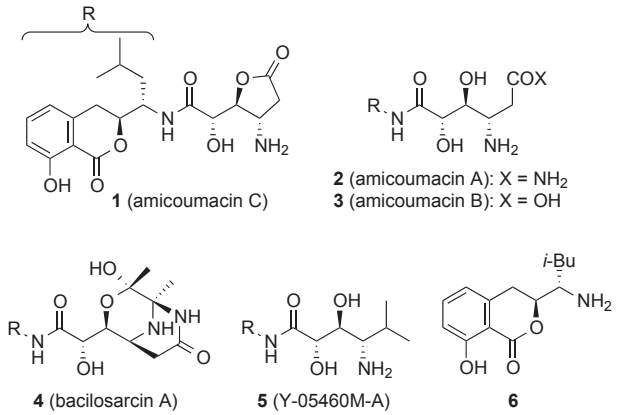

Fig. 1. Amicoumacin C (**1**) and related compounds.

Members of this family are produced mainly by bacteria of genus *Bacillus* and share the same left-hand amine segment (**6**) in common, while the right-hand acid portion shows considerable structural diversity, as exemplified by **1**, amicoumacins A (**2**) and B (**3**),[1,2,4] bacilosarcin A (**4**),[5] and Y-05460M-A (**5**).[6] Many of this class of natural products are known to have various medicinally or agriculturally important biological properties such as antibacterial, anti-inflammatory, antiulcer, cytotoxic, and herbicidal activities.[1–7] These intriguing physiological effects as well as the unique molecular architectures prompted synthetic efforts toward this family of natural products, which culminated in the total synthesis of the antiulcer natural product amiocumacin B (**3**) (also called AI-77-B) by Shioiri's and six other laboratories.[8–14] We also succeeded in the total synthesis of bacilosarcin A (**4**) and its analog (bacilosarcin B) as well as amicoumacins A (**2**) and B (**3**) by using amicoumacin C (**1**) as a common synthetic intermediate,[15] and, additionally, Y-05460M-A (**5**) and its higher homolog (PM-94128) by a different synthetic approach.[16]

Among the eight total syntheses of **3** reported so far,[8–15] four syntheses including the first one by Shioiri and co-workers utilized diastereoselective addition of metalated aromatic esters **A** to Boc-protected leucinal **B** for the synthesis of amine segment precursors **C** (Scheme 1).[8,10,11,14] This type of reactions, though concise, faced critical problems concerning the chemical yield (32–64%), diastereoselectivity at the newly formed C3 stereogenic center (3β/3α=2.2:1–81:19),[17] and reproducibility; the low reproducibility of this transformation was also posed in another synthetic study on **3**.[9] The amine segment employed in our total synthesis of **1**–**5** and

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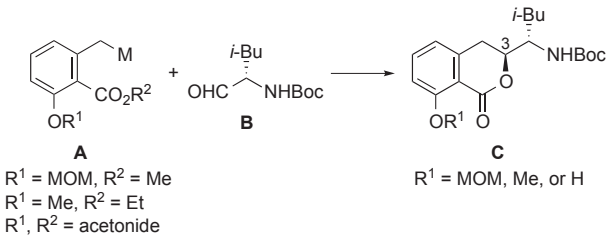


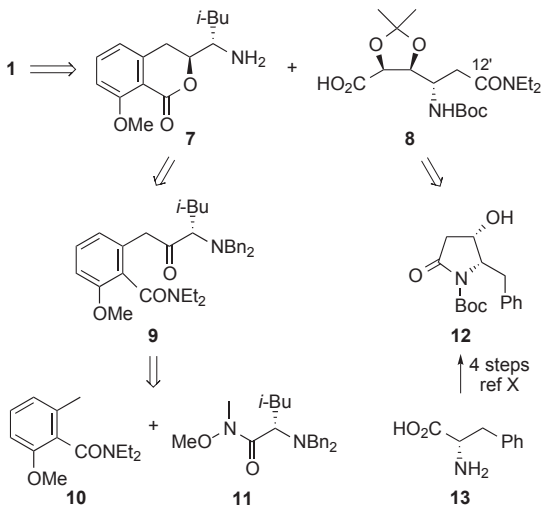
Scheme 1. Key steps in previous syntheses of amine segment precursors **C**.

related natural products was, on the other hand, prepared via BF_3-promoted ring opening of a chiral epoxide intermediate with an aromatic nucleophile as the key carbon–carbon bond-forming step,[15,16] which also, however, resulted in a modest yield of 48%. We describe herein a new total synthesis of amicoumacin C (**1**) that includes an efficient construction of the methyl ether of the amine segment **6** via highly diastereoselective reduction of an α-dibenzylamino ketone intermediate.

2. Results and discussion

2.1. Retrosynthetic analysis of 1

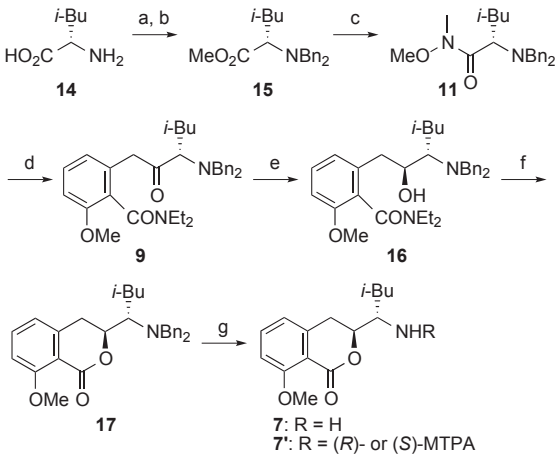
Scheme 2 outlines our retrosynthetic analysis of **1**. The amide **1** should be obtainable via condensation of amine segment **7** and acid segment **8**. To prepare **7** in a stereoselective manner, we planed to utilize a highly diastereoselective reduction of α-dibenzylamino ketone **9** under non-chelation control. The ketone **9** would be derived by acylation of the benzylic position of *N*,*N*-diethyl amide **10** with Weinreb's amide **11**; we expected that a benzylic anion generated from **10** would be stable enough to realize its efficient addition to **11**, unlike the corresponding anion prepared from ester precursors (**A** in Scheme 1). The preparation of the acid segment **8**, on the other hand, is based primarily on our protocol previously employed for the total synthesis of Y-05460M-A (**5**) and PM-94128, except for additional installation of the amide functionality at the C12′ position.[16,17] Thus, compound **8** was traced back to known hydroxy lactam **12** obtainable from L-phenylalanine **13** by a convenient 4-step sequence of reactions; compound **12** would be convertible into **8** via stereoselective dihydroxylation of an α,β-unsaturated lactam intermediate derived from **12** and oxidative cleavage of the benzene ring to form a carboxylic acid as the key steps.



Scheme 2. Retrosynthetic analysis of **1**.

2.2. Preparation of amine segment 7

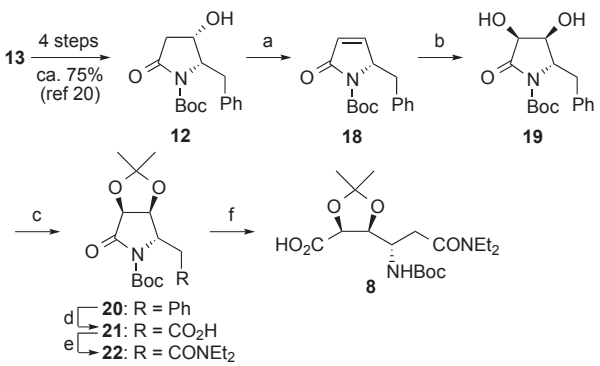
The preparation of **7** commenced with the conversion of L-leucine **14** into the corresponding methyl ester, which upon exposure to benzyl bromide in DMF in the presence of the Hünig base provided *N*,*N*-dibenzyl-protected leucinate **15** in an excellent yield of 98% for the two steps (Scheme 3).[18] The ester **15** was derivatized into Weinreb's amide **11** and then allowed to react with the benzyllithium species generated by treating **10** with *s*-BuLi in THF. The resulting ketone **9** obtained in 77% overall yield from **15** was subjected to highly diastereoselective reduction under non-chelation-controlled conditions ($NaBH_4$ in MeOH) developed by Reetz and co-workers to afford **16**.[19,20] Refluxing a solution of **16** in toluene under acidic conditions gave lactone **17**,[21] the hydrogenolytic debenzylation of which provided the amine segment **7** in 56% yield for the three steps from **9**. The amino lactone **7** was evaluated to be optically pure by ^1H NMR analysis of the corresponding (*R*)- and (*S*)-MTPA amides **7′**.



Scheme 3. Preparation of amine segment **7**. Reagents and conditions: (a) $SOCl_2$, MeOH, reflux, 3 h; (b) BnBr, *i*-Pr_2NEt, DMF, 0 °C to rt, 12 h, 98% from **14**; (c) Me(MeO)NH·HCl, *i*-PrMgCl, THF, −20 °C to rt, 5 h, 84%; (d) **10**, *s*-BuLi, THF, −78 °C, 25 min, 92%; (e) $NaBH_4$, MeOH, 0 °C to rt, 23 h; (f) CSA, toluene, reflux, 3 d, 70% from **9**; (g) H_2, Pd/C, HCl/MeOH, EtOAc, rt, 16 h, 80%.

2.3. Preparation of acid segment 8

The acid segment **8** was prepared in 6 steps from the known *N*-protected hydroxyl lactam **12** which, in turn, was obtainable in ca. 75% yield from L-leucine by a 4-step sequence involving the acylation of Meldrum's acid with *N*-Boc-L-leucine (Scheme 4).[16,22] Subjection of **12** to a one-pot mesylation/elimination protocol gave dehydration product **18** in 80% yield. Dihydroxylation of the double bond of **18**



Scheme 4. Preparation of acid segment **8**. Reagents and conditions: (a) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 20 h, 80%; (b) OsO_4, NMO, citric acid, MeCN/Me_2CO/H_2O, rt, 18 h; (c) $Me_2C(OMe)_2$, TsOH·H_2O, CH_2Cl_2, rt, 24 h, 84% from **18**; (d) $RuCl_3 \cdot nH_2O$, $NaIO_4$, $NaHCO_3$, EtOAc/MeCN/H_2O, rt, 3 d; (e) Et_2NH, EDC·HCl, HOBt, DMAP, CH_2Cl_2, rt, 24 h, 60% from **20**; (f) LiOH·H_2O, THF/H_2O, rt, 13 h.

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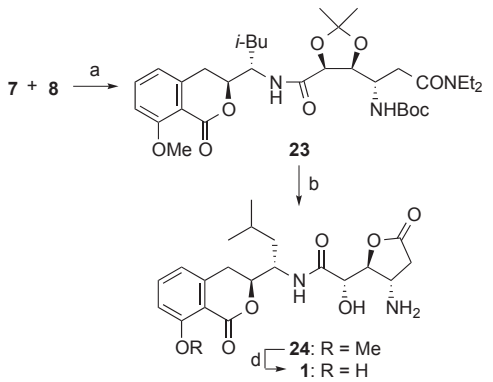
from the less hindered β-face of the ring system provided diol **19**, the protection of which as an acetonide furnished **20** in 84% yield for the two steps. The benzene ring of **20** was then cleaved oxidatively by Sharpless' method using a catalytic amount of $RuCl_3$ to give carboxylic acid **21**,[23] which was condensed with diethylamine to afford **22** in 60% yield from **20**. Finally, selective hydrolytic opening of the *N*-Boc-protected lactam ring of **22** furnished the acid segment **8**.

2.4. Completion of the total synthesis of 1

The final stage of our total synthesis of amicoumacin C (**1**) is shown in Scheme 5. Condensation of **7** and **8** proceeded smoothly by exposing the two segments to HBTU/Et_3N in CH_2Cl_2/DMF, providing amide **23** in a good overall yield of 85% from **22**. Removal of the acetonide and Boc protecting groups of **23** under acidic conditions brought about concomitant lactone ring formation to give **24** in 75% yield, and subsequent unmasking of the methyl-protected phenolic hydroxy group by treatment with BBr_3 in CH_2Cl_2 in the presence of anisole provided amicoumacin C (**1**) in 87% yield.[15a,24] The ^1H and ^{13}C NMR spectra of **1** were identical with those of an authentic material,[15a] and the specific rotation of **1** [$[\alpha]_D^{25}$ −120 (*c* 0.070, MeOH)] showed good agreement with a reported value [$[\alpha]_D^{22}$ −123 (*c* 0.045, MeOH)].[15a]



Scheme 5. Synthesis of amicoumacin C (**1**). Reagents and conditions: (a) HBTU, Et_3N, CH_2Cl_2/DMF, rt, 12 h, 85% from **22**; (b) 12 M HCl, DME, 85 °C, 3 d, 75%; (c) BBr_3, anisole, CH_2Cl_2, −78 to −5 °C, 12 h, 87%.

3. Conclusion

In conclusion, the stereoselective total synthesis of amicoumacin C (**1**) was accomplished in 17% overall yield from L-phenylalanine **13** by a 13-step sequence. The amine segment **7**, which is common in all members of the amicoumacin family of natural products, was prepared stereoselectively from L-leucine in 42% yield through 7 steps by making use of the highly diastereoselective reduction of the α-dibenzylamino ketone **9**. The oxidative cleavage of the benzene ring of **20** to form the carboxylic acid **21** as well as the acidic hydrolysis of the acetonide protecting group of the amide **23** accompanied by concomitant lactone ring formation were also employed as the key transformations in the present synthesis. Synthetic studies on some amicoumacin family of natural products using **1** as the pivotal intermediate are now in progress and will be reported in due course.

4. Experimental section

4.1. General

IR spectra were recorded by a Jasco FT/IR-4100 spectrometer using an ATR (ZnSe) attachment. NMR spectra were recorded with TMS as an internal standard in $CDCl_3$ by a Varian MR-400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C) unless otherwise stated. Optical rotation values were measured with a Jasco P-2200 polarimeter, and the mass spectra were obtained with Jeol JMS-700 spectrometer operated in the FAB mode. Melting points were determined with a Yanaco MP-J3 apparatus and are uncorrected. Merck silica gel 60 (63–200 μm) was used for column chromatography. Analytical thin-layer chromatography was performed using Merck silica gel 60 F_{254} plates (0.25 mm thick). Solvents for reactions were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, MeCN, and DMF from CaH_2; MeOH from $Mg(OMe)_2$; toluene from $LiAlH_4$. All air- or moisture-sensitive reactions were conducted under a nitrogen atmosphere.

4.2. Methyl *N*,*N*-dibenzyl-L-leucinate (15)

To a stirred solution of L-leucine (**14**) (4.00 g, 30.5 mmol) in MeOH (60 mL) was added dropwise $SOCl_2$ (5.50 mL, 75.4 mmol) at 0 °C. The mixture was stirred at reflux for 3 h, and then concentrated in vacuo to give an ester intermediate as a white power, which was taken up in DMF (43 mL). To the solution was added *i*-Pr_2NEt (31.9 mL, 183 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. BnBr (10.9 mL, 91.5 mmol) was then added, and the resulting mixture was gradually warmed to room temperature and stirred for 12 h. The mixture was diluted with water and extracted with hexane/EtOAc (1:1). The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc/toluene=48:1:1) to give **15** (9.69 g, 98% from **14**) as a colorless oil. $[\alpha]_D^{23}$ −120 (*c* 1.12, $CHCl_3$); IR: ν_{max} 1732 (s), 1495 (m), 1145 (s), 697 (vs); ^1H NMR: δ 0.60 (3H, d, *J*=6.6 Hz), 0.81 (3H, d, *J*=6.6 Hz), 1.44–1.52 (1H, m), 1.64–1.72 (1H, m), 1.72–1.82 (1H, m), 3.39 (1H, dd, *J*=8.6, 6.1 Hz), 3.50 (2H, d, *J*=13.9 Hz), 3.75 (3H, s), 3.91 (2H, d, *J*=13.9 Hz), 7.23 (2H, t, *J*=7.2 Hz), 7.31 (4H, dd, *J*=7.5, 7.2 Hz), 7.35 (4H, d, *J*=7.5 Hz); ^{13}C NMR: δ 21.5, 23.2, 24.4, 38.8, 51.0, 54.5 (2C), 58.7, 126.9 (2C), 128.2 (4C), 128.9 (4C), 139.7 (2C), 173.9; HRMS (FAB): *m*/*z* calcd for $C_{21}H_{28}NO_2$ ($[M+H]^+$) 326.2120, found 326.2122.

4.3. (*S*)-2-(Dibenzylamino)-*N*-methoxy-*N*,4-dimethylpentanamide (11)

To a stirred solution of MeN(OMe)·HCl (3.45 g, 35.4 mmol) in THF (40 mL) was added dropwise as a solution of *i*-PrMgCl (2.0 M in THF, 33 mL, 66 mmol) at 0 °C and the mixture was stirred at the same temperature for 15 min. A solution of **15** (7.67 g, 23.6 mmol) in THF (40 mL) was then added, and the resulting mixture was stirred for 2 h at 0 °C. The mixture was gradually warmed to room temperature and stirred for 5 h. The mixture was quenched with saturated aq NH_4Cl and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc=5:1) to give **11** (7.00 g, 84%) as a colorless oil. $[\alpha]_D^{23}$ +19.5 (*c* 1.26, $CHCl_3$); IR: ν_{max} 3028 (w), 1494 (m), 1661 (s); ^1H NMR: δ 0.79 (3H, d, *J*=6.6 Hz), 0.88 (3H, d, *J*=6.6 Hz), 1.44–1.56 (1H, m), 1.72–1.92 (2H, m), 3.13 (3H, s), 3.18 (3H, s), 3.75 (2H, d, *J*=14.2 Hz), 3.85 (1H, br s), 3.96 (2H, br d, *J*=14.2 Hz), 7.20 (2H, t, *J*=7.3 Hz), 7.28 (4H, dd, *J*=7.5, 7.3 Hz), 7.38 (4H, d, *J*=7.5 Hz); ^{13}C NMR: δ 21.7, 23.2, 24.3, 31.8, 37.3, 54.4 (2C), 54.8, 60.6, 126.6 (2C), 128.0 (4C), 128.7 (4C), 140.4 (2C), 175.5; HRMS (FAB): *m*/*z* calcd for $C_{22}H_{31}N_2O_2Na$ ($[M+Na]^+$) 355.2385, found 355.2386.

4.4. (*S*)-2-[3-(Dibenzylamino)-5-methyl-2-oxohexyl]-*N*,*N*-diethyl-6-methoxybenzamide (9)

To a stirred solution of *s*-BuLi (1.0 M in hexane, 8.4 mL, 8.4 mmol) in THF (7.0 mL) was added a solution of **10** (1.89 g,

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8.54 mmol) in THF (18.0 mL) at −78 °C and stirred for 1 h at the same temperature. A solution of **11** (1.48 g, 4.16 mmol) in THF (17 mL) was then added, and the resulting mixture was stirred for 25 min. The mixture was quenched with saturated aq NH_4Cl and extracted with EtOAc. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc=5:1) to give **9** as a ca. 3:2 atropisomeric mixture (1.97 g, 92%). $[\alpha]_D^{27}$ −80.1 (*c* 0.765, $CHCl_3$); IR: ν_{max} 1718 (m), 1629 (s), 1584 (m), 1262 (m); ^{1}H NMR: δ 0.77 (3H, d, *J*=6.4 Hz), 0.80 (3H, d, *J*=6.4 Hz), 1.00 (0.6×3H, t, *J*=7.2 Hz), 1.02 (0.4×3H, t, *J*=7.2 Hz), 1.06 (0.6×3H, t, *J*=7.2 Hz), 1.13 (0.4×3H, t, *J*=7.2 Hz), 1.37–1.56 (2H, m), 1.64–1.76 (1H, m), 2.94–3.85 (13.4H, m), 4.01 (0.6×1H, d, *J*=18.4 Hz), 6.46 (0.4×1H, d, *J*=7.7 Hz), 6.67 (0.6×1H, d, *J*=7.7 Hz), 6.75 (0.4×1H, d, *J*=8.4 Hz), 6.78 (0.6×1H, d, *J*=8.4 Hz), 7.17 (0.6×1H, t, *J*=8.1 Hz), 7.21–7.39 (10.4H, m); ^{13}C NMR: δ 12.7, 13.3/13.6, 22.4/22.5, 22.8/23.1, 25.3/25.4, 32.4/32.6, 38.1/38.3, 42.7, 44.9/45.1, 54.5 (2C), 55.4, 63.8/64.4, 109.0, 122.9, 123.4, 127.1/127.2 (2C), 128.36/128.42 (4C), 128.8/129.0 (4C), 129.1/129.2, 133.0/133.3, 139.45/139.49 (2C), 155.4, 167.6/167.7, 208.2/208.5; HRMS (FAB): *m*/*z* calcd for $C_{33}H_{43}N_2O_3$ ($[M+H]^+$) 515.3274, found 515.3273.

4.5. (*S*)-3-[(*S*)-1-(Dibenzylamino)-3-methylbutyl]-8-methoxyisochroman-1-one (17)

To a stirred solution of **9** (0.861 g, 1.67 mmol) in MeOH (12.0 mL) was added portionwise $NaBH_4$ (0.384 g, 10.2 mmol) at 0 °C. The mixture was gradually warmed to room temperature and stirred for 22.5 h. The mixture was quenched with saturated aq NH_4Cl and extracted with EtOAc. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **16**, which was dissolved in toluene (15 mL). The solution was mixed with camphor sulfonic acid (1.21 g, 5.21 mmol) at room temperature, and the resulting mixture was stirred at 110 °C for 3 days. After cooling to room temperature, the mixture was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc=2:1) to give **17** (0.520 g, 70% from **9**) as a white solid. Mp 55.0–58.0 °C; $[\alpha]_D^{28}$ −138 (*c* 1.23, $CHCl_3$); IR: ν_{max} 1728 (s), 1597 (w), 1235 (m), 1089 (s), 698 (s); ^{1}H NMR: δ 0.79 (3H, d, *J*=6.5 Hz), 0.82 (3H, d, *J*=6.5 Hz), 1.48–1.56 (1H, m), 1.62–1.76 (2H, m), 2.38 (1H, dd, *J*=16.4, 2.3 Hz), 2.75–2.81 (1H, m), 3.42 (1H, dd, *J*=16.4, 12.0 Hz), 3.55 (2H, d, *J*=13.4 Hz), 3.94 (3H, s), 4.06 (2H, d, *J*=13.4 Hz), 4.44 (1H, ddd, *J*=11.9, 4.6, 2.4 Hz), 6.76 (1H, d, *J*=7.6 Hz), 6.89 (1H, d, *J*=8.6 Hz), 7.22 (2H, t, *J*=7.2 Hz), 7.29 (4H, t, *J*=7.2 Hz), 7.36 (4H, d, *J*=7.2 Hz), 7.42 (1H, t, *J*=8.6, 7.6 Hz); ^{13}C NMR: δ 22.4, 23.2, 24.7, 32.7, 33.5, 55.1 (2C), 56.1, 56.4, 79.5, 110.6, 113.8, 119.3, 126.8 (2C), 128.1 (4C), 129.1 (4C), 134.3, 140.4 (2C), 143.0, 161.1, 162.5; HRMS (FAB): *m*/*z* calcd for $C_{29}H_{34}NO_3$ ($[M+H]^+$) 444.2539, found 444.2538.

4.6. (*S*)-3-[(*S*)-1-Amino-3-methylbutyl]-8-methoxyisochroman-1-one (7)

A mixture of **17** (0.276 g, 0.622 mmol), 10% Pd/C (0.264 g), and a HCl solution (1.25 M in MeOH, 1.87 mL, 2.33 mmol) in EtOAc/MeOH (1:1, 7 mL) was stirred at room temperature for 15.5 h under a hydrogen atmosphere. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was diluted with $CHCl_3$ and mixed well with saturated aq $NaHCO_3$ (5 drops) and solid $NaHCO_3$. The mixture was concentrated in vacuo, and the residue was purified by SiO_2 column chromatography ($CHCl_3$/MeOH=1:0–50:1) to give **7** (0.131 g, 80%) as a pale yellow oil. $[\alpha]_D^{27}$ −104 (*c* 0.53, MeOH); IR: ν_{max} 1728 (s), 1599 (m), 1476 (m), 1239 (m), 1083 (m); ^{1}H NMR: δ 0.92 (3H, d, *J*=6.4 Hz), 0.96 (3H, d, *J*=6.7 Hz), 1.30–1.38 (1H, m), 1.38–1.47 (1H, m), 1.47–1.62 (2H, br s, NH_2), 1.75–1.88 (1H, m), 2.80 (1H, dd, *J*=16.0, 2.2 Hz), 2.95–3.02 (1H, m), 3.12 (1H, dd, *J*=16.0, 12.6 Hz), 3.94 (3H, s), 4.19 (1H, ddd, *J*=12.6, 5.0, 2.2 Hz), 6.83 (1H, d, *J*=7.6 Hz), 6.92 (1H, d, *J*=8.4 Hz), 7.46 (1H, t, *J*=8.4, 7.6 Hz); ^{13}C NMR: δ 21.3, 23.4, 24.2, 31.3, 42.4, 51.7, 56.0, 81.6, 110.6, 113.4, 119.2, 134.3, 141.9, 160.9, 162.4; HRMS (FAB): *m*/*z* calcd for $C_{15}H_{22}NO_3$ ($[M+H]^+$) 264.1600, found 264.1603.

4.7. Determination of the enantiomeric excess of 7

Compound **7** was converted into the corresponding (*R*)- and (*S*)-MTPA amides (**7′**) by treating with 5.0 equiv of (*S*)- and (*R*)-MTPACl, respectively, in pyridine overnight at room temperature; the disappearance of the starting material **7** was checked by TLC. The C3 methine proton of the (*R*)-MTPA amide were observed as a deformed triplet (*J*=6.1 Hz) at δ 5.49 in ^{1}H NMR (400 MHz, $CDCl_3$), while that of the (*S*)-MTPA amide was detected at δ 5.59 as a deformed triplet (*J*=5.8 Hz). Comparison of the two spectra indicated that the enantiomeric excess of **7** was virtually 100%.

4.8. *tert*-Butyl (*S*)-2-benzyl-5-oxo-2,5-dihydro-1*H*-pyrrole-1-carboxylate (18)

To a stirred solution of **12** (1.67 g, 5.73 mmol) and Et_3N (2.40 mL, 17.2 mmol) in CH_2Cl_2 (45.0 mL) was added MsCl (0.76 mL, 9.8 mmol) at 0 °C. The mixture was gradually warmed to room temperature and stirred for 20 h. The mixture was quenched with saturated aq NH_4Cl at 0 °C and extracted with ether. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc=3:1) to give **18** (1.26 g, 80%) as a pale yellow solid. Mp 92.0–93.0 °C; $[\alpha]_D^{20}$ +224 (*c* 1.11, $CHCl_3$); IR: ν_{max} 1762 (s), 1712 (w), 1688 (w), 1284 (m), 1150 (s); ^{1}H NMR: δ 1.63 (9H, s), 2.74 (1H, dd, *J*=13.1, 9.5 Hz), 3.54 (1H, dd, *J*=13.1, 3.7 Hz), 4.72–4.78 (1H, m), 6.02 (1H, dd, *J*=6.1, 1.6 Hz), 7.03 (1H, dd, *J*=6.1, 1.4 Hz), 7.12–7.17 (2H, m), 7.23–7.34 (3H, m); ^{13}C NMR: δ 28.2 (3C), 38.5, 63.3, 83.1, 126.6, 127.1, 128.6 (2C), 129.3 (2C), 135.5, 149.4, 149.9, 169.0; HRMS (FAB): *m*/*z* calcd for $C_{16}H_{20}NO_3$ ($[M+H]^+$) 274.1443, found 274.1444.

4.9. *tert*-Butyl (3a*S*,4*S*,6a*S*)-4-benzyl-2,2-dimethyl-6-oxotetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate (20)

To a stirred solution of **18** (0.950 g, 3.48 mmol) in MeCN/acetone/H_2O (1:1:1, 15 mL) were successively added *N*-methylmorpholine *N*-oxide (0.814 g, 6.95 mmol), citric acid (0.668 g, 3.48 mmol), and OsO_4 (44.0 mg, 0.173 mmol) at room temperature. After 18 h of stirring, the mixture was diluted with saturated aq NH_4Cl at 0 °C and extracted with $CHCl_3$. The extract was successively washed with saturated aq $Na_2S_2O_3$, 5% aq citric acid, water and brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **19**, which was taken up in CH_2Cl_2 (9.3 mL). To the solution were added $TsOH\cdot H_2O$ (70 mg, 0.37 mmol) and $Me_2C(OMe)_2$ (14.3 mL, 116 mmol) at room temperature. The mixture was stirred at room temperature for 24 h and then poured into saturated aq $NaHCO_3$. The resulting mixture was extracted with ether and the extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc=5:1–2:1) to give **20** (1.01 g, 84% from **18**) as a white solid. Mp 113.0–115.0 °C; $[\alpha]_D^{21}$ +73.2 (*c* 1.02, $CHCl_3$); IR: ν_{max} 1781 (s), 1703 (m), 1493 (w), 1148 (vs), 1104 (s); ^{1}H NMR: δ 1.29 (3H, s), 1.40 (3H, s), 1.61 (9H, s), 2.93 (1H, dd, *J*=14.1, 7.4 Hz), 3.11 (1H, dd, *J*=14.1, 3.2 Hz), 3.90 (1H, d, *J*=5.0 Hz), 4.39 (1H, d, *J*=5.0 Hz), 4.48 (1H, dd, *J*=7.4, 3.2 Hz), 7.14 (2H, d, *J*=7.6 Hz), 7.25–7.36 (3H, m); ^{13}C NMR: δ 25.8, 27.1, 28.0 (3C), 37.8, 60.6, 75.3, 76.8, 83.8, 112.2, 127.4, 129.0 (2C), 129.4 (2C), 135.2, 149.7, 170.9;

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HRMS (FAB): m/z calcd for $C_{19}H_{26}NO_5$ ($[M+H]^+$) 348.1811, found 348.1809.

4.10. *tert*-Butyl (3a*S*,4*S*,6a*S*)-4-[2-(diethylamino)-2-oxoethyl]-2,2-dimethyl-6-oxotetrahydro-5*H*-[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylate (22)

To a stirred mixture of **20** (0.295 g, 0.849 mmol) and $NaIO_4$ (2.57 g, 12.0 mmol) in EtOAc/MeCN/water (1:1:5, 21 mL) were added $RuCl_3 \cdot xH_2O$ (0.025 g) and $NaHCO_3$ (0.025 g, 0.298 mmol), and the resulting mixture was stirred vigorously for 3 days. The mixture was filtered through a pad of Celite, and the filtrate was extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **21**, which was then dissolved in CH_2Cl_2 (8.0 mL). To the solution were added EDCI·HCl (140 mg, 0.730 mmol) and HOBt (110 mg, 0.814 mmol) at −10 °C. DMAP (90.0 mg, 0.737 mmol) and Et_2NH (0.14 mL, 1.4 mmol) were then added, and the resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with 5% aq citric acid and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography (hexane/EtOAc=1:1) to give **22** (0.188 g, 60% from **20**) as a white solid. Mp 93.0–95.0 °C; $[\alpha]_D^{23}$ +72.9 (c 1.11, $CHCl_3$); IR: ν_{max} 1784 (s), 1701 (w), 1632 (s), 1230 (s), 1153 (vs); ^{1}H NMR: δ 1.08 (3H, t, J=7.2 Hz), 1.16 (3H, t, J=7.2 Hz), 1.36 (3H, s), 1.46 (3H, s), 1.54 (9H, s), 2.69 (1H, dd, J=16.4, 2.5 Hz), 3.10 (1H, dd, J=16.4, 6.5 Hz), 3.21–3.33 (3H, m), 3.33–3.43 (1H, m), 4.36 (1H, dd, J=6.5, 2.5 Hz), 4.72 (1H, d, J=5.8 Hz), 4.98 (1H, d, J=5.8 Hz); ^{13}C NMR: δ 13.0, 14.2, 25.2, 26.8, 28.0 (3C), 33.8, 40.0, 41.9, 58.8, 76.9, 78.4, 83.6, 112.1, 150.4, 168.0, 170.9; HRMS (FAB): m/z calcd for $C_{18}H_{31}N_2O_6$ ($[M+H]^+$) 371.2183, found 371.2184.

4.11. *tert*-Butyl {(*S*)-3-(diethylamino)-1-[(4*S*,5*S*)-5-({(*S*)-1-[(*S*)-8-methoxy-1-oxoisochroman-3-yl]-3-methylbutyl}carbamoyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-oxopropyl}carbamate (23)

To a stirred solution of **22** (0.295 g, 0.796 mmol) in THF (4.0 mL) were added water (2.0 mL) and LiOH·H_2O (0.145 g, 3.46 mmol) at room temperature. After 12.5 h, the mixture was quenched with 2 M aq HCl and extracted with EtOAc. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give crude **8** (0.282 g, ca. 91% yield). Then, a solution of crude **8** (0.252 g, ca. 0.649 mmol) in CH_2Cl_2/DMF (5:2, 11.2 mL) and a solution of **7** (0.194 g, 0.737 mmol) in CH_2Cl_2/DMF (5:2, 11.2 mL) were successively added to a mixture of HBTU (0.295 g, 0.778 mmol) and Et_3N (180 μL, 1.29 mmol) in CH_2Cl_2/DMF (3.5:1, 10.3 mL) at 0 °C. The mixture was gradually warmed to room temperature and stirred for 12 h. The mixture was diluted with water and extracted with CH_2Cl_2. The extract was successively washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography ($CHCl_3$/MeOH=1:0–250:1) to give **23** (0.383 g, 85% from **22**) as a colorless oil. $[\alpha]_D^{25}$ −80.0 (c 1.26, $CHCl_3$); IR: ν_{max} 3413 (w), 1724 (s), 1673 (m), 1634 (m), 1599 (m), 1477 (s), 1239 (s); ^{1}H NMR: δ 0.96 (6H, br t, J=6.9 Hz), 1.10 (3H, t, J=7.1 Hz), 1.18 (3H, t, J=7.1 Hz), 1.36 (3H, s), 1.41 (9H, s), 1.54 (3H, s), 1.58–1.76 (2H, m), 1.90–1.96 (1H, m), 2.62 (1H, dd, J=15.5, 4.9 Hz), 2.77 (1H, dd, J=16.3, 2.1 Hz), 3.03–3.12 (1H, m), 3.25–3.45 (4H, m), 3.95 (3H, s), 4.05–4.15 (1H, m), 4.29–4.37 (1H, m), 4.46 (1H, br d, J=12.4 Hz), 4.57 (1H, d, J=7.0 Hz), 4.78 (1H, br t, J=7.3 Hz), 5.64 (1H, br d, J=7.5 Hz, NH), 6.81 (1H, d, J=7.4 Hz), 6.91 (2H, br d, J=8.4 Hz, Ar–H and NH), 7.45 (1H, dd, J=8.4, 7.4 Hz); ^{13}C NMR: δ 13.0, 14.3, 22.5, 24.66, 24.74, 27.1, 28.3 (3C), 31.5, 31.8, 33.2, 40.1, 40.8, 42.0, 48.4, 48.6, 56.1, 76.6, 77.7, 78.5, 78.9, 109.6, 110.7, 113.3, 119.4, 134.7, 142.1, 155.4, 161.1, 162.3, 169.6, 170.0; HRMS (FAB): m/z calcd for $C_{33}H_{52}N_3O_9$ ($[M+H]^+$) 634.3703, found 634.3705.

4.12. (*S*)-2-[(2*S*,3*S*)-3-Amino-5-oxotetrahydrofuran-2-yl]-2-hydroxy-*N*-{(*S*)-1-[(*S*)-8-methoxy-1-oxoisochroman-3-yl]-3-methylbutyl}acetamide (24)

To a stirred solution of **23** (21.0 mg, 0.0331 mmol) in DME (1.0 mL) was added one drop of 12 M aq HCl at room temperature. The mixture was heated at reflux for 3 days and then concentrated in vacuo. The residue was diluted with $CHCl_3$ and mixed well with saturated aq $NaHCO_3$ (5 drops) and solid $NaHCO_3$. The mixture was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by SiO_2 column chromatography ($CHCl_3$/MeOH=1:0–20:1) to give **24** (10.4 mg, 75%) as a pale yellow oil. $[\alpha]_D^{25}$ −123 (c 0.940, $CHCl_3$); IR: ν_{max} 3353 (m), 1778 (m), 1723 (s), 1669 (m), 1599 (m), 1239 (m); ^{1}H NMR: δ 0.93 (3H, d, J=6.5 Hz), 0.96 (3H, d, J=6.6 Hz), 1.40–1.72 (4H, m), 1.41–1.50 (1H, m), 1.80–1.88 (1H, m), 2.30 (1H, dd, J=18.0, 4.5 Hz), 2.79 (1H, br d, J=16.2 Hz), 2.95 (1H, dd, J=18.0, 8.0 Hz), 3.01 (1H, dd, J=16.2, 12.5 Hz), 3.74–3.80 (1H, m), 3.94 (3H, s), 4.29–4.39 (1H, m), 4.44 (1H, br d, J=12.5 Hz), 4.55 (1H, d, J=3.3 Hz), 4.64 (1H, t, J=3.3 Hz), 6.79 (1H, d, J=7.4 Hz), 6.90 (1H, d, J=8.2 Hz), 7.11 (1H, d, J=9.6 Hz, CONH, 7.44 (1H, dd, J=8.2, 7.4 Hz); ^{13}C NMR: δ 21.7, 23.1, 24.8, 31.7, 38.6, 40.2, 48.2, 49.1, 56.2, 71.5, 79.3, 88.2, 110.8, 113.1, 119.4, 134.9, 141.8, 161.1, 162.6, 170.3, 176.3; HRMS (FAB): m/z calcd for $C_{21}H_{29}N_2O_7$ ($[M+H]^+$) 421.1974, found 421.1975.

4.13. (*S*)-2-[(2*S*,3*S*)-3-Amino-5-oxotetrahydrofuran-2-yl]-2-hydroxy-*N*-{(*S*)-1-[(*S*)-8-hydroxy-1-oxoisochroman-3-yl]-3-methylbutyl}acetamide (amicoumacin C) (1)

To a stirred solution of **24** (10.4 mg, 0.0247 mmol) in CH_2Cl_2 (2.4 mL) were successively added anisole (22 μL, 0.20 mmol) and BBr_3 (1.0 M in CH_2Cl_2, 0.10 mL, 0.1 mmol) at −78 °C. After 12 h of stirring, the mixture was gradually warmed to −5 °C and stirred for 12 h. The mixture was quenched by the addition of saturated aq $NaHCO_3$ and solid $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by SiO_2 column chromatography ($CHCl_3$/MeOH=1:0–10:1) to give **1** (8.7 mg, 87%) as a colorless oil. $[\alpha]_D^{25}$ −120 (c 0.070, MeOH); IR: ν_{max} 3271 (m), 1794 (m), 1675 (vs), 1618 (s), 1202 (s); ^{1}H NMR (CD_3OD): δ 0.93 (3H, d, J=6.5 Hz), 0.99 (3H, d, J=6.6 Hz), 1.39–1.47 (1H, m), 1.61–1.74 (1H, m), 1.78–1.86 (1H, m), 2.24 (1H, dd, J=18.0, 3.2 Hz), 2.94 (1H, dd, J=18.0, 7.9 Hz), 2.96–3.05 (2H, m), 3.72–3.77 (1H, m), 4.32 (1H, dt, J=11.0, 4.3 Hz), 4.39 (1H, d, J=2.9 Hz), 4.55 (1H, t, J=2.9 Hz), 4.65 (1H, dt, J=10.4, 4.3 Hz), 6.80 (1H, d, J=7.2 Hz), 6.84 (1H, d, J=8.6 Hz), 7.46 (1H, dd, J=8.6, 7.2 Hz); ^{13}C NMR (CD_3OD): δ 21.8, 23.8, 26.0, 30.9, 38.8, 40.5, 40.9, 50.5, 73.1, 82.7, 90.0, 109.4, 116.8, 119.6, 137.6, 141.3, 163.2, 171.0, 173.2, 178.5; HRMS (FAB, negative ion mode): m/z calcd for $C_{20}H_{25}N_2O_7$ ($[M-H]^-$) 405.1662, found 405.1663.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra for new compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.02.014. These data include MOL file and InChiKey of the most important compounds described in this article.

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21. The transformation of amide **l0** into lactone **17** (Scheme 3) proceeded in 64% overall yield without any need for separation of diastereomers, although it required 3 steps. On the other hand, esters **A** gave lactones **C** in a single operation (Scheme 1), but the conversions necessitated bothersome chromatographic separation of diastereomers and resulted in low isolated yields of 26% (R^1=MOM, R^2=Me),[8] 23% (R^1=Me, R^2=Et),[10] and 45% (R^1, R^2=acetonide).[14] Moreover, as mentioned in Refs. 9 and 10, the direct conversion of **A** into **C** seems to have a problem in reproducibility, while our three-step conversion of **10** into **17** is highly reproducible and considered to be more amenable to scale-up. From these viewpoints, we think our three-step protocol via ketone intermediate **9** is more efficient and practical than the single-step conversion depicted in Scheme 1.
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