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Tandem *N*-acyliminium/Pictet–Spengler/intramolecular Diels–Alder reaction: an expedient route to hexacyclic tetrahydro-β-carbolines

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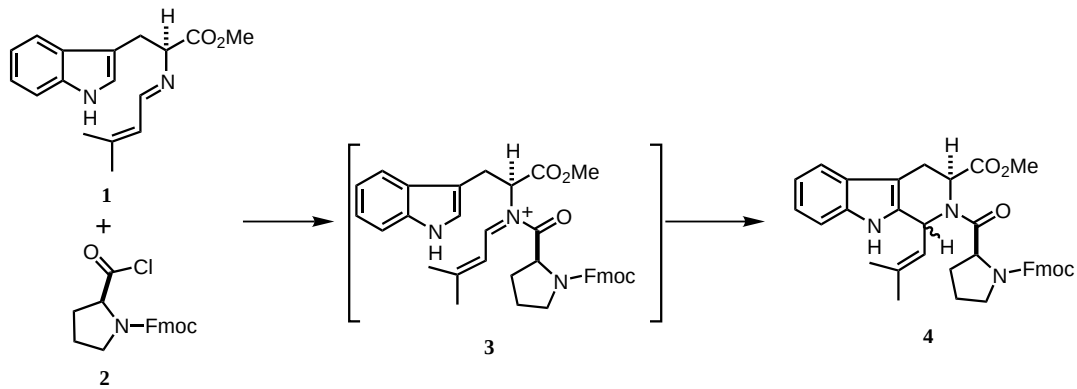
Abstract—A mild and efficient synthesis of rigid hexacyclic nitrogen heterocycles with tetrahydro-β-carboline skeleton is described. Acylation of the imines **7a–d**, prepared from tryptamine (**5**) and furaldehydes **6a–d**, with maleic anhydride at room temperature provided the corresponding hexacyclic nitrogen heterocycles **10a–d** via a tandem *N*-acyliminium/Pictet–Spengler/IMDA reaction. In this tandem approach, five stereocenters, including a quaternary center and three rings are generated with excellent stereoselectivity. Key to the success of this approach is the use of furaldehyde and maleic anhydride as the aldehyde and anhydride components, respectively. Transformation of the free acid to the corresponding amide, ester and alcohol is also studied.

The Pictet–Spengler (P–S) condensation reaction[1] has emerged as one of the most powerful carbon–carbon bond forming methods for the rapid construction of molecules with tetrahydro-β-carboline[2] and tetrahydroisoquinoline[3] frameworks under mild reaction conditions. Combinations of various reactions with P–S condensation in a sequential/tandem fashion has been studied by several research groups and successfully utilized in organic synthesis.[4] For example, Ganesan et al. and Nakagawa et al. reported an efficient one-pot synthesis of acylated tetrahydro-β-carboline **4** enroute to demethoxyfumitremorgin C through acylation of the imine **1** with Fmoc-L-proline acid chloride **2** (Scheme 1).[4a,b] The product is reported to form via a two-step one-pot reaction sequence: (1) acylation of the imine **1** initially gives an *N*-acyliminium intermediate **3**, which immediately undergoes (2) the P–S condensation to provide the tetrahydro-β-carboline **4**, via a spiroindolenine intermediate, as a mixture of diastereoisomers. On the basis of the above reports and our recent work on intramolecular Diels–Alder (IMDA) reaction employing furan as a diene partner,[5,6] we envisioned that acylation of the imine **7**, prepared from furaldehyde **6** and tryptamine **5**, with maleic anhydride would



Scheme 1.

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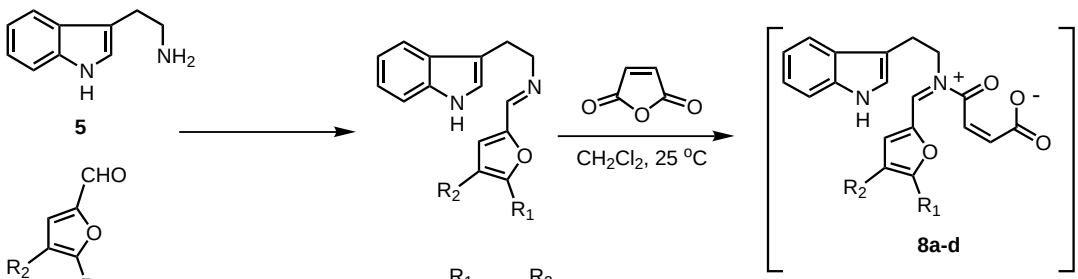
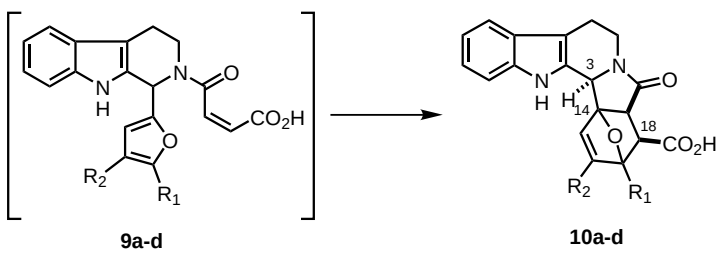
first give an *N*-acyliminium ion **8**,[7,8] which could then undergo the P–S condensation reaction to provide the acylated tetrahydro-β-carboline **9** (Scheme 2). Since the P–S condensation product **9** contains a diene and an activated dienophile acid suitably aligned in close proximity, the triene **9** would be expected to undergo a [4+2] cycloaddition under mild conditions to provide a novel rigid hexacyclic nitrogen heterocycle **10** (Scheme 2). This approach would allow for rapid and efficient construction of structurally and stereochemically complex molecules with multiple stereocenters and rings under mild conditions in a tandem fashion from readily available achiral starting materials, which is extremely valuable in organic synthesis.[9] Herein, we wish to communicate the first report on tandem *N*-acyliminium/Pictet–Spengler/IMDA reaction.

The imine **7a** was chosen as the model substrate to carry out our initial optimization study. The requisite imine **7a** was readily prepared from condensation of tryptamine **5** and 2-furaldehyde **6a** in benzene. After removal of the solvent, the crude imine **7a** was dissolved in CH_2Cl_2 and allowed to react with 1.1 equiv. of maleic anhydride at room temperature for 24 h (Scheme 2). As predicted, the reaction proceeded smoothly and yielded the expected hexacyclic lactam acid **10a** as a single diasteroisomer in 80% crude yield after filtration and washing (CH_2Cl_2). Since the crude acid **10a** was isolated in analytically pure form, no further effort was taken to purify the crude acid **10a**. Compound **10a** was fully characterized by ^1H, ^{13}C NMR and HRMS and the relative *cis* stereochemistry at C-18 and C-19 was determined based on the coupling constant of H_{18} and H_{19} in the ^1H NMR ($J_{18,19}$ = 9.2 Hz). The structure of compound **10a** was further confirmed based on the X-ray crystal structure of a related compound.[10] The high diastereoselectivity observed in this tandem approach presumably results from the approach of the dienophile from the less-hindered face (opposite to the indole group) in an *exo* fashion. To the best of our knowledge, this is the first example of preparation of hexacyclic nitrogen heterocycle in a single step from acylation of the imine **7a** with maleic anhydride. In this tandem approach, five stereocenters, including a quaternary center, and three rings are generated with excellent stereoselectivity. Stereoselective construction of multiple stereocenters and rings in a single step is very attractive and synthetically useful for rapid assembly of complex polycyclic natural and unnatural molecules. The key to the success of this tandem approach is the use of furaldehyde and maleic anhydride as the aldehyde and acid anhydride components, respectively. This tandem approach avoids the use of an acid catalyst and higher temperatures to promote the P–S condensation reaction. In addition, use of maleic anhydride introduces a free acid function-



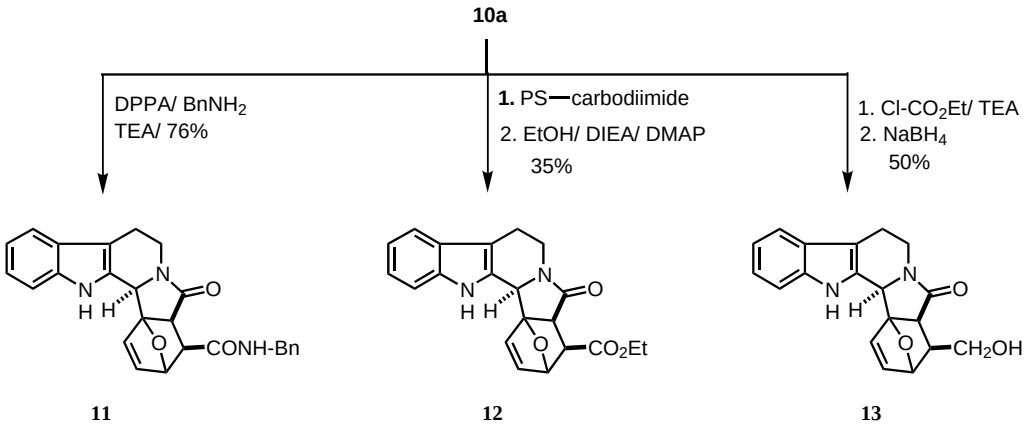
	R_1	R_2
6a	H	H
6b	Me	H
6c	CH_2OAc	H
6d	Me	Me

	R_1	R_2
7a	H	H
7b	Me	H
7c	CH_2OAc	H
7d	Me	Me



	R_1	R_2	Yield (%)
10a	H	H	80
10b	Me	H	80
10c	CH_2OAc	H	76
10d	Me	Me	60

Scheme 2.



Scheme 3.

ality, which could be used as a handle to increase the structural diversity.

Having isolated the rigid hexacyclic lactam acid **10a** in a two-step one-pot approach, we then briefly examined the influence of the substituents at C-4 and C-5 positions of the furan ring on this tandem reaction by employing various substituted furaldehydes **6b–d** (Scheme 2). Accordingly, the imines **7b–d**, prepared from the amine **5** and aldehydes **6b–d**, were dissolved in CH_2Cl_2 and treated with maleic anhydride to yield the corresponding lactam acids **10b–d** (Scheme 2). Isolation of the lactam acids **10b–d** in moderate to good crude yields indicated that substituents at the C–4 and C-5 positions did not have any major impact during the [4+2] cycloaddition. Furthermore, the C-5 substituent on the furan ring introduces an additional quaternary center at C-17 of the lactams **10b–d**.

To increase the synthetic scope and utility of our tandem approach, chemical modification of the free acid in lactam **10a** was then investigated (Scheme 3). Reaction of the acid **10a** with benzyl amine in the presence of diphenylphosphoryl azide (DPPA) and triethylamine (TEA) at room temperature provided the corresponding amide **11** in 76% yield after purification. Activation of the acid **10a** with *N*-cyclohexylcarbodiimide, *N′*-methyl polystyrene (solid-supported carbodiimide, Novabiochem, loading 1.49 mmol/g) followed by treatment with EtOH (excess), *N*,*N*-diisopropylethylamine (DIEA, 2.0 equiv.) and 4-(dimethylamino)pyridine (DMAP, cat.) provided the ester **12** in 35% yield after purification. Commercial availability of large numbers of diverse amines and alcohols makes this post-modification strategy very attractive for the construction of libraries of natural product like molecules in a short period of time. Reduction of the acid **10a** to the corresponding alcohol **13** was also examined. Treatment of the acid **10a** with ethyl chloroformate and TEA followed by reduction with $NaBH_4$ yielded the corresponding alcohol **13** in 50% yield after purification.

In summary, we have described an efficient synthesis of hexacyclic lactam acids with tetrahydro-β-carboline motif via acylation of the imines **7a–d**, prepared from tryptamine **5** and furaldehydes **6a–d**, with maleic anhydride. The products are formed via a tandem *N*-acyliminium/Pictet-Spengler/IMDA reaction. In this tandem approach, five stereocenters, including a quaternary center and three rings are generated with excellent stereoselectivity. Transformation of the acid **10a** to the corresponding amide, ester and alcohol was also examined. Wider selection of commercially available amines and alcohols makes this a valuable approach to prepare highly diversified libraries of nitrogen heterocycles with tetrahydro-β-carboline skeleton. Currently, we are investigating the tandem *N*-acyliminium/P–S/IMDA reaction with a wide range of amines known to undergo P–S condensation reaction and the results will be reported in due course.

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References

1. For review on Pictet–Spengler Condensation Reaction, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
2. (a) Cox, E. D.; Hamaker, L. K.; Li, J.; Yu, P.; Czerwinski, M.; Deng, L.; Bennett, D. W.; Cook, J. M.; Watson, W. H.; Krawiec, M. *J. Org. Chem.* **1997**, *62*, 44 and references cited therein; (b) Leonard, J. *Nat. Prod. Rev.* **1999**, *16*, 319; (c) Love, B. E. *Org. Prep. Proced. Int.* **1996**, 3; (d) Magnus, P.; Westlund, N. *Tetrahedron Lett.* **2000**, *41*, 9369; (e) Bailey, P. D.; Cochrane, P. J.; Forster, A. H.; Morgan, K. M.; Pearson, D. P. J. *Tetrahedron Lett.* **1999**, *40*, 4597; (f) Bailey, P. D.; Cochrane, P. J.; Lorenz, K.; Collier, I. D.; Pearson, D. P. J.; Rosair, G. M. *Tetrahedron Lett.* **2001**, *42*, 113; (g) Madrigal, A.; Grande, M.; Avendano, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3515; (h) Gremmen, C.; Willemse, B.; Wanner, M. J. M.; Koomen, G. *Org. Lett.* **2000**, *2*, 1955; (i) Yu, S.; Berner, M.; Cook, J. M. *J. Am. Chem. Soc.* **2000**, *122*,

7827; (j) Brown, R. T.; Dauda, B. E. N.; Jameson, S. B.; Santos, C. A. M. *Tetrahedron Lett*. **2000**, *41*, 8861; (k) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. *J. Org. Chem*. **1998**, *63*, 6348.

3. (a) Vicario, J. L.; Badia, D.; Dominguez, E.; Carrillio, L. *J. Org. Chem*. **1999**, *64*, 4610; (b) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc*. **1999**, *121*, 8401; (c) Vicario, J. L.; Badia, D.; Dominguez, E.; Crespo, A.; Carrillo, L. *Tetrahedron: Asymmetry* **1999**, *10*, 1947; (d) Czarnocki, Z.; Mieczkowski, J. B.; Kiegiel, J.; Arazny, Z. *Tetrahedron: Asymmetry* **1995**, *6*, 2899; (e) Prat, L.; Bureau, R.; Daveu, C.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *J. Heterocyclic Chem*. **2000**, *37*, 767; (f) Brozda, D.; Koroniak, L.; Rozwadowska, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 3017; (g) Carrillo, L.; Badia, D.; Dominguez, E.; Anakabe, E.; Osante, I.; Tellitu, I.; Vicario, J. L. *J. Org. Chem*. **1999**, *64*, 1115; (h) Piper, I. M.; MacLean, D. B.; Kvarnstorm, I.; Szarek, W. A. *Can. J. Chem*. **1983**, *61*, 2721.
4. (a) Wang, H.; Ganesan, A. *Tetrahedron Lett*. **1997**, *38*, 4327; (b) Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Kodato, S.; Une, T.; Taniguchi, M.; Hino, T. *Tetrahedron Lett*. **1986**, *27*, 3235; (c) Leonard, J.; Hague, A. B.; Harms, G.; Jones, M. F. *Tetrahedron Lett*. **1999**, *40*, 8141; (d) Leonard, J.; Appleton, D.; Fearnley, S. P. *Tetrahedron Lett*. **1994**, *35*, 1071; (e) Leonard, J.; Hague, A. B.; Jones, M. F. *Tetrahedron Lett*. **1997**, *38*, 3071; (f) Leonard, J.; Fearnley, S. P.; Hickey, D. M. B. *Synlett* **1992**, 272; (g) Leonard, J.; Fearnley, S. P.; Hague, A. B.; Wong, G.; Jones, M. F. *Tetrahedron Lett*. **1997**, *38*, 3067; (h) Dondas, H. A.; Duraisingham, J.; Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Thornton-Pett, M.; Sridharan, V.; Suganthan, S. *Tetrahedron* **2000**, *56*, 4063; (i) Grigg, R.; Thornton-Pett, M.; Yoganathan, G. *Tetrahedron* **1999**, *55*, 8129; (j) Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Sridharan, V.; Suganthan, S.; Thornton-Pett, M.; Zhang, J. *Tetrahedron* **2000**, *56*, 6585; (k) Ohba, M.; Kubo, H.; Fuiji, T.; Ishibashi, H.; Sargent, M. V.; Arbain, D. *Tetrahedron Lett*. **1997**, *38*, 6697; (l) Wang, H.; Usui, T.; Osada, H.; Ganesan, A. *J. Med. Chem*. **2000**, *43*, 1577.
5. (a) Paulvannan, K. *Tetrahedron Lett*. **1999**, *40*, 1851; (b) Paulvannan, K.; Jacobs, J. W. *Tetrahedron* **1999**, *55*, 7433; (c) Paulvannan, K.; Chen, T.; Jacobs, J. W. *Synlett* **1999**, 1609.
6. For reviews on IMDA reaction, see: (a) Ciganek, E. *Org. React*. **1984**, *32*, 1; (b) Craig, D. *Chem. Soc. Rev*. **1987**, *16*, 187; (c) Lipshutz, B. H. *Chem. Rev*. **1986**, *86*, 795; (d) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521.
7. For reviews on *N*-acyliminum chemistry, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817; (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
8. For generation of *N*-acyliminum ion via acylation of imine with cyclic anhydride, see: (a) van Alphen, J. *Rec. Trav. Chim. Pays-Bas* **1942**, *61*, 895; (b) Castagnoli, N. *J. Org. Chem*. **1969**, *34*, 3187; (c) Cushman, M.; Castagnoli, N. *J. Org. Chem*. **1971**, *36*, 3404; (d) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem*. **1977**, *42*, 1111; (e) Cushman, M.; Abbaspour, A.; Gupta, Y. P. *J. Am. Chem. Soc*. **1983**, *105*, 2873; (f) Cushman, M.; Wong, W. C. *J. Org. Chem*. **1984**, *49*, 1278; (g) Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron* **1977**, *33*, 331.
9. For reviews on tandem reactions, see: (a) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103; (b) Ho, T. L. *Tandem Organic Reactions*; Wiley: New York, 1992; (c) *Frontiers in Organic Synthesis*; Wender, P. A., Ed.; *Chem. Rev*. **1996**, *96*, 1–600; (d) Neuschutz, K.; Velker, J.; Neier, R. *Synthesis* **1998**, 227; (e) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 131; (f) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M.; Stoddart, J. F.; Vogtle, F.; Eds.; Wiley-VCH: Weinheim, 2000; pp. 39–64.
10. Compound prepared from acylation of the imine **7a** with acid chloride of fumaric acid monoethyl ester. Unpublished result.

Typical experimental procedure for the preparation of 10a: To a solution of amine **5** (10.0 g, 62.4 mmol, 1.0 equiv.) in benzene was added aldehyde **6a** (6.59 g, 68.7 mmol, 1.1 equiv.) and the reaction mixture was stirred at room temperature for 15 h. Solvent was removed to give the crude imine **7a**, which was used in the next step without further purification. To a solution of the crude imine **7a** (1.0 g, 4.2 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) was added maleic anhydride (0.45 g, 4.62 mmol, 1.1 equiv.) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and the solid was washed with CH_2Cl_2 (3×) to yield the acid **10a**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.50 (m, 1H), 2.51 (d, $J=9.2$ Hz, 1H), 2.77 (m, 1H), 2.97 (m, 1H), 3.03 (d, $J=9.2$ Hz, 1H), 4.28 (dd, $J=13.0$, 5.5 Hz, 1H), 4.86 (d, $J=1.8$ Hz, 1H), 5.6 (s, 1H), 6.49 (dd, $J=5.9$, 1.8 Hz, 1H), 6.81 (d, $J=5.9$ Hz, 1H), 6.97 (td, $J=7.0$, 1.1 Hz, 1H), 7.06 (td, $J=7.0$, 1.1 Hz, 1H), 7.33 (d, $J=8.1$ Hz, 1H), 7.41 (d, $J=8.1$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.9, 36.8, 44.9, 51.0, 54.9, 80.7, 90.6, 108.0, 111.2, 117.7, 118.5, 121.1, 126.3, 129.0, 135.2, 136.4, 136.8, 137.2, 169.1, 172.8; HRMS calcd for $C_{19}H_{16}N_2O_4$ 336.1110, found: 336.1102.

Preparation of compound 11: To a suspension of the acid **10a** (0.84 mmol, 1.0 equiv.) in DMF (7 mL) were added $BnNH_2$ (0.14 g, 1.26 mmol, 1.5 equiv.), DPPA (0.35 g, 1.26 mmol, 1.5 equiv.) and TEA (0.138, 1.26 mmol, 1.5 equiv.) and the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted with ethyl acetate (25 mL) and washed with water (4×25 mL). The organic layer was dried, filtered, evaporated and purified by column chromatography to give **11**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.46 (m, 1H), 2.59 (d, $J=9.0$ Hz, 1H), 2.74 (dd, $J=15.0$, 4.0 Hz, 1H), 2.96 (d, $J=9.0$ Hz, 1H), 3.01 (dd, $J=12.0$, 4.0 Hz, 1H), 4.17 (dd, $J=15.0$, 5.1 Hz, 1H), 4.33 (m, 2H), 4.91 (d, $J=1.8$ Hz, 1H), 5.58 (s, 1H), 6.51 (dd, $J=5.9$, 1.8 Hz, 1H), 6.82 (d, $J=5.9$ Hz, 1H), 6.96 (td, $J=7.0$, 1.1 Hz, 1H), 7.04 (td, $J=7.0$, 1.1 Hz, 1H), 7.19–7.35 (m, 6H), 7.37 (d, $J=7.7$ Hz, 1H), 7.82 (t, $J=5.1$ Hz, 1H), 10.86 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8, 36.8, 42.6, 45.7, 51.0, 53.8, 80.9, 90.3, 107.9, 111.0, 117.4, 118.3, 120.8, 126.1, 126.5, 127.3, 127.9, 128.7, 135.7, 136.2, 139.1, 168.8, 169.8; HRMS calcd for $C_{26}H_{23}N_3O_3$ 425.1739, found: 425.1744.

Preparation of compound 12: To a suspension of the acid **10a** (0.55 g, 1.65 mmol, 1.0 equiv.) in NMP (15 mL) was

added *N*-cyclohexylcarbodiimide, *N'*-methyl polystyrene (3.5 g, 4.95 mmol, 3.0 equiv., loading 1.49 mmol/g, Novabiochem) and the reaction mixture was agitated at room temperature for 45 min and then filtered. To a suspension of the resin in CH_2Cl_2 were added ethanol (2 mL, excess), DIEA (0.43 g, 3.3 mmol, 2.0 equiv.) and DMAP (cat) and the reaction mixture was agitated at room temperature for 12 h and then filtered. The filtrate was concentrated and then purified by column chromatography to give compound **12**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (t, $J=7.0$ Hz, 3H), 2.74 (d, $J=9.1$ Hz, 1H), 2.80–2.90 (m, 2H), 3.00 (d, $J=9.1$ Hz, 1H), 3.07 (m, 1H), 4.22 (m, 2H), 4.56 (m, 1H), 5.12 (d, $J=1.6$ Hz, 1H), 5.46 (s, 1H), 6.58 (dd, $J=5.9$, 1.6 Hz, 1H), 6.75 (d, $J=5.9$ Hz, 1H), 7.10 (m, 1H), 7.16 (m, 1H), 7.30 (d, $J=8.1$ Hz, 1H), 7.48 (d, $J=7.7$ Hz, 1H), 7.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 21.3, 37.9, 45.3, 52.1, 54.9, 61.4, 81.7, 90.5, 110.9, 111.3, 118.6, 119.9, 122.5m 127.0, 127.5, 134.3, 136.9, 138.8, 169.2, 171.4; HRMS calcd for $C_{21}H_{20}N_2O_4$ 364.1423, found: 364.1413.

Preparation of compound 13: To a suspension of the acid **10a** (0.1 g, 0.3 mmol, 1 equiv.) in THF (6 mL) at –20°C were added ethyl chloroformate (40 mg, 0.36 mmol, 1.2 equiv.) and TEA (46 mg, 0.45 mmol, 1.5 equiv.) and the reaction mixture was stirred at 0°C for 1 h. To the reaction mixture at 0°C were slowly added solid $NaBH_4$ (30 mg, 0.6 mmol, 2 equiv.) and MeOH (2 mL) and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was diluted with EtOAc and washed with $NaHCO_3$. The organic layer was dried, filtered, evaporated and purified by column chromatography to give compound **13**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (m, 1H), 2.91 (m, 3H), 3.12 (m, 1H), 3.67 (td, $J=11.4$, 2.6 Hz, 1H), 3.82 (td, $J=11.4$, 4.4 Hz, 1H), 4.61 (m, 2H), 5.05 (dd, $J=11.0$, 1.8 Hz, 1H), 5.46 (s, 1H), 6.61 (d, $J=5.9$ Hz, 1H), 6.65 (d, $J=5.9$ Hz, 1H), 7.09 (t, $J=7.5$ Hz, 1H), 7.15 (t, $J=7.5$ Hz, 1H), 7.29 (d, $J=8.1$ Hz, 1H), 7.47 (d, $J=8.1$ Hz, 1H), 7.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 38.0, 44.9, 51.8, 55.7, 64.7, 81.4, 91.6, 110.5, 111.4, 118.8, 120.1, 122.7, 126.9, 127.5, 132.7, 137.0, 139.5, 172.4; HRMS calcd for $C_{19}H_{18}N_2O_3$ 322.1317, found: 322.1308.