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Access to the noryohimban [6,5,6,5,6] ring system via an intramolecular furan Diels–Alder reaction

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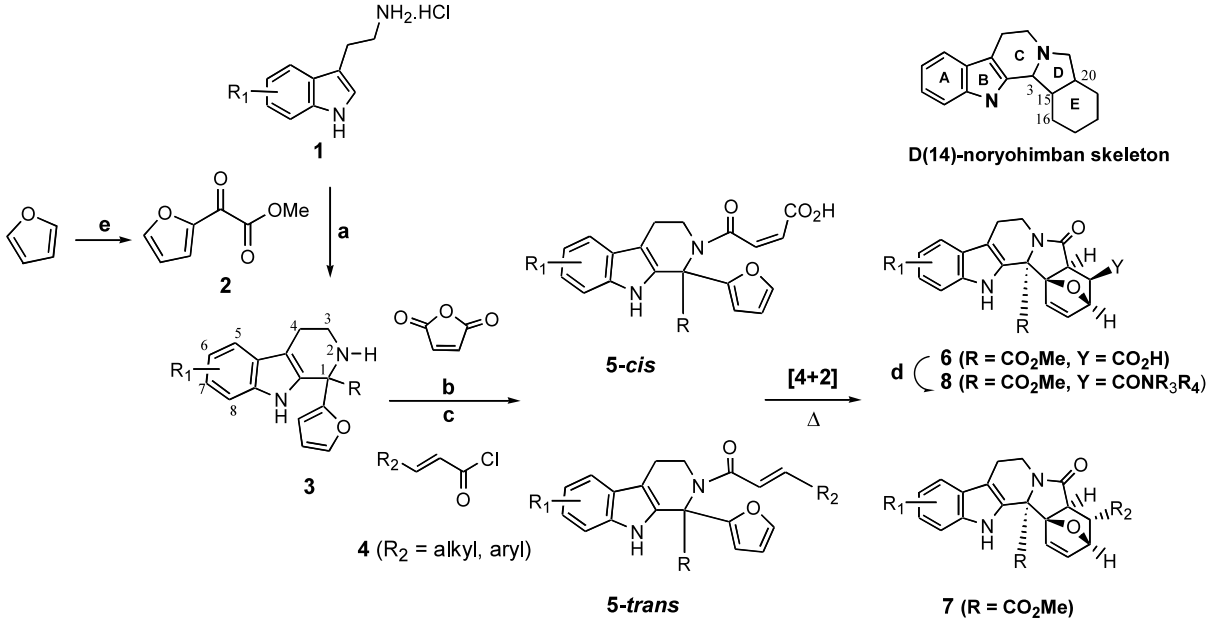
Abstract—Polycyclic indolic compounds containing the [6,5,6,5,6] ring system were prepared via an intramolecular furan Diels–Alder reaction of α,β-unsaturated amides generated by the *N*-acylation of 1-(2-furyl)-β-tetrahydrocarbolines. This chemistry can provide access to D(14)-noryohimban derivatives by exploiting the functionality on the C,D,E ring system of the corresponding cycloadducts.

Polycyclic indole alkaloids continue to be the target of scientific investigations because of their interesting physiological, biological and structural properties.[1] In our search for libraries of rigid heterocycles we turned our attention to the noryohimban [6,5,6,5,6] ring system since very little is known about the biological activities of this unnatural ring system and its analogs, in contrast with the well studied yohimbine alkaloids.

The polycyclic indolic [6,5,6,5,6] ring system is usually constructed by the reductive cyclization[2] of *N*-imido tryptamines or by the condensation of tryptamines with 2-carboxybenzaldehyde equivalents.[3] However, the molecules generated by these methods lack any immediate functionality for further manipulation or introduction of diversity. Here, we wish to report our studies leading to functionalized indole polycycles that give access to D(14)-noryohimban derivatives.



Scheme 1. *Reagents and conditions*: (a) MeOH, 60°C; (b) $(CH_2)_2Cl_2$, 70°C, 24 h; (c) THF, N*i*Pr$_2$Et, rt to 60°C; (d) CH_3CN, HBTU, R_3R_4NH, NEt_3; (e) *n*-BuLi, THF, −78°C, HMPA, CuI then $ClCOCO_2Me$.

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We envisioned[4] that *N*-acylation of a secondary furfurylamine such as β-tetrahydrocarboline **3** (β-THC) with maleic anhydride[5] would result in the activated maleamide **5-*cis***, which could undergo an intramolecular furan Diels–Alder cycloaddition (IMDAF)[6] to give carboxylic acid **6**. Similarly, *N*-acylation of **3** with acid chloride **4** followed by an IMDAF cycloaddition of the intermediate α,β-unsaturated amide **5-*trans*** would give compound **7** (Scheme 1). If this were the case, then entry to hexacyclic heterocycles **6** and **7** would require the synthesis of **3**.

A direct route to β-THC **3** (R = H) would involve the Pictet–Spengler reaction of tryptamine **1** with 2-furaldehyde. However, the instability of the requisite furaldehydes and products towards acidic conditions makes these substrates inaccessible by this route. We found that the disubstituted 1-(2-furyl)-1-carboxymethyl-β-tetrahydrocarboline **3** (R = CO_2Me) was particularly stable and readily available by a Pictet–Spengler condensation of tryptamine hydrochloride **1** with the furyl-α-ketoester **2** (Scheme 1). Eight different substrates were prepared in good yields (40–73%, Table 1) from eight commercially available tryptamines and α-ketoester **2**.[7] Ketoester **2** was prepared in multi-gram quantities from furan in 40–50% yield via a lithiation, transmetallation with CuI, and quenching the corresponding cuprate with methyl oxalyl chloride.[8]

As we had hoped, when disubstituted tetrahydrocarboline **3** was treated with maleic anhydride in dichloroethane (DCE) at 70°C, carboxylic acid **6** was formed as the sole product. Acid **6** could then be converted cleanly to amide **8** (Table 1, entries 6–8) upon treatment with an amine in the presence of HBTU, as shown in Scheme 1, thus introducing an additional element of diversity.

We also found that *N*-acylation of **3** with a crotonyl or cinnamoyl chloride **4** at room temperature afforded the α,β-unsaturated amide **5-*trans***, which converged to cycloadduct **7** upon heating at 60°C for 5 h (Table 1, entries 1–5). However, electron-withdrawing substituents on the phenyl ring of cinnamoyl chlorides facilitated the cycloaddition process and the corresponding cycloadducts were formed even after stirring the reaction mixture at room temperature overnight (entries 4 and 5). Although similar intramolecular Diels–Alder reactions of furans with α,β-unsaturated amides[9] are usually accelerated by internal hydrogen bonding, internal coordination with a Lewis acid catalyst or excessive heating, cyclization of α,β-unsaturated amide **5-*trans*** is presumably entropically favored due to the rigid tether and the *gem*-disubstitution effect.[10]

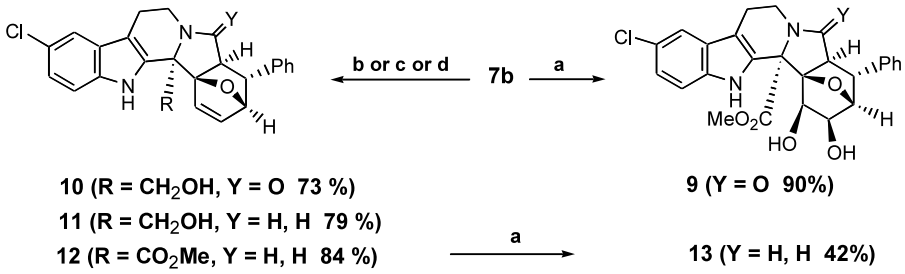
The cycloaddition proceeds in a stereocontrolled fashion where an *exo*-addition of the furan nucleus to the dienophile prevails. The transition state presumably involves a conformation where the ester group lies *anti* to the furan oxygen due to unfavorable steric repulsions between the ester carbonyl and the lone pair of electrons on the furan oxygen. The stereochemical outcome of the cycloaddition was determined by a single X-ray crystal structure of compound **7a**.[12]

Cycloadducts **6** and **7** contain functionalities, which allow access to new noryohimban derivatives (Scheme 2). For instance, dihydroxylation of the olefin **7b** (conditions a) gave diol **9** while reduction of the ester group gave alcohol **10** (conditions b). Reduction of both the

Table 1.

Entry	β-THC (Yield%[a])	Product	Yield[a] (%)
1	**3a** R_1 = 6-H (64)	**7a** R_2 = Ph	90
2	**3b** R_1 = 6-Cl (55)	**7b** R_2 = Ph	94
3	**3c** R_1 = 6-OH (62)	**7c** R_2 = Me	70
4	**3d** R_1 = 6-OBn (73)	**7d** R_2 = (2-Cl)Ph	86
5	**3e** R_1 = 7-F (60)	**7e** R_2 = (3-CF_3)Ph	79
6	**3f** R_1 = 6-OMe (70)	**8a** R_3–R_4 = -$(CH_2)_2$NPh(3-CF_3)$(CH_2)_2$-	72
7	**3g** R_1 = 6-Me (65)	**8b** R_3 = isobutyl, R_4 = H	77
8	**3h** R_1 = 6-Br (40)	**8c** R_3 = Ph, R_4 = H	85

[a] Isolated yields of purified products. All compounds gave satisfactory ^{1}H NMR and mass spectra.[11]



Scheme 2. *Reagents and conditions*: (a) OsO_4 (cat.), NMMO, acetone–H_2O (4:1); (b) EtOH, $NaBH_4$; (c) $Me_3O^+BF_4^-$, CH_2Cl_2 at rt then EtOH, $NaBH_4$; (d) $Me_3O^+BF_4^-$, CH_2Cl_2 at rt then MeOH, $NaBH_4$, 0°C to rt.

amido carbonyl and the ester group of cycloadduct **7b**, without cleavage of the oxygen bridge of the oxabicyclo ring system, gave noryohimban **11** (conditions c). Selective reduction of the amido carbonyl of **7b** gave noryohimban **12** (conditions d), which was also converted to diol **13** (conditions a).

The functionality of intermediates **6**, **7**, and **8** is amenable to further chemical diversification through solution phase parallel synthesis methods[13] utilizing the chemistry depicted in Scheme 1. The preparation of screening libraries utilizing these compounds as building blocks towards the synthesis of highly functionalized noryohimban derivatives is currently under investigation and will be communicated in due course.

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6. For a review on the synthetic applications of IMDAF, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179–14233.
7. A solution of tryptamine hydrochloride (1 equiv.) and ketoester **2** (1.5 equiv.) in MeOH (MeOH–AcOH when R_1 = 5-OBn) was heated at 60°C overnight. The mixture was concentrated and the resulting residue was partitioned between $CHCl_3$ and 1N NaOH. The organic layer was isolated and the aqueous basic phase was washed with $CHCl_3$. The combined organic layer was then dried over Na_2SO_4 and concentrated to give the desired β-THC **3**. It could be further purified, if necessary, by a quick filtration of an EtOAc or $CHCl_3$ solution over silica gel. ^{1}H NMR (300 MHz, $CDCl_3$) for **3a**: δ 8.48 (s, 1H), 7.55 (d, 1H, J = 8.0 Hz), 7.40 (s, 1H), 7.38 (d, 1H, J = 8.0 Hz), 7.23 (t, 1H, J = 7.7 Hz), 7.12 (t, 1H, J = 7.7 Hz), 6.30 (m, 1H), 6.15 (d, 1H, J = 3.3 Hz), 3.88 (s, 3H), 3.25 (m, 1H), 3.10 (m, 1H), 2.82 (t, 2H, J = 5.2, J = 6.0 Hz).
8. For the synthesis of **2** via the oxidation of the corresponding α-hydroxy ester, see: (a) Tanaka, M.; Kobayashi, T.; Sakakura, T. *Angew. Chem., Int. Ed. Engl*. **1984**, *23*, 518; (b) Monenschein, H.; Drager, G.; Jung, A.; Kirschning, A. *Chem. Eur. J*. **1999**, *5*, 2270–2280. Large quantities of ketoester **2** were made by metallation of furan as described below: To a dry 2 L three neck round bottom flask, equipped with a magnetic stirrer, immersion thermometer, addition funnel and gas inlet, 600 mL dry THF and furan (27 g, 0.4 mol) were added. The stirred solution was cooled to −70°C followed by addition of HMPA (90 g, 0.5 mol) and 160 mL of 2.5 M *n*-BuLi (0.4 mol). After the mixture was stirred at −70°C for 1 h, CuI (76 g, 0.4 mol) was added and the cooling bath was removed. After the stirred mixture was warmed up to −20°C and CuI dissolved, the resulting dark homogeneous mixture was cooled to −70°C. MeOCOCOCl (50 g, 0.41 mol) was then added dropwise and the mixture was warmed up to room temperature. After stirring overnight, the mixture was diluted with toluene (500 mL), quenched with water (500 mL) and then filtered. After washing the filter cake with toluene (100 mL), the organic phase of the filtrate was separated and the aqueous layer was extracted with toluene. The combined organic layer was washed with water, dried over Na_2SO_4 and concentrated. Vacuum distillation of the resulting residue afforded 25 g (40%) of ketoester **2** as a yellowish oil which rapidly solidified. Bp 135°C/20 mm Hg. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (m, 2H), 6.62 (m, 1H), 3.98 (s, 3H).
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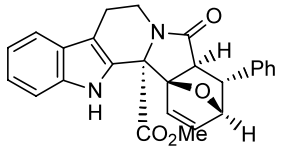
10. For substitution effects in the intramolecular furan Diels–Alder reaction, see: Jung, M. E.; Kiankarimi, M. *J. Org. Chem*. **1998**, *63*, 2968–2974 and references cited therein.
11. **Typical experimental procedure for the synthesis of cycloadducts 7**: To a solution of β-THC **3** (1 equiv.) and N*i*Pr$_2$Et (1.2 equiv.) in THF (1:1 acetone–THF for **3c**) at room temperature, acid chloride **4** (1.1 equiv.) was added. The reaction mixture was stirred at room temperature overnight and then heated at 60°C for 4–5 h. The reaction mixture was then concentrated and the resulting residue dissolved in $CHCl_3$ and washed with 1N HCl and aq. $NaHCO_3$. The organic phase was then isolated, dried over Na_2SO_4, filtered and concentrated to give the crude product. Purification by silica gel flash chromatography or preparative TLC with EtOAC–Hex as eluent afforded the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) for **7a**: δ 8.35 (s, 1H), 7.50 (d, 1H, J = 8.0 Hz), 7.37 (d, 1H, J = 8.2 Hz), 7.30–7.05 (m, 7H), 6.80 (d, 1H, J = 5.8 Hz), 6.40 (d, 1H, J = 6.0 Hz), 5.12 (d, 1H, J = 4.4 Hz), 4.65 (dd, 1H, J = 4.7, J = 12.9 Hz), 3.92 (s, 3H), 3.85 (t, 1H, J = 4.1, J = 4.4 Hz), 3.18 (m, 1H), 3.02–2.80 (m, 3H).
Typical experimental procedure for the synthesis of cycloadducts 8: A solution of β-THC **3** (1 equiv.) and maleic anhydride (1.2 equiv.) in DCE (2:1 CH_3CN–DCE for **3c**) was heated at 70°C for 24 h. The reaction mixture was concentrated to give acid **6** which was then dissolved in CH_3CN and treated consecutively with an amine (1.2 equiv.), NEt_3 (2 equiv.) and HBTU (1.2 equiv.). After stirring at room temperature overnight, the reaction mixture was concentrated and the resulting residue dissolved

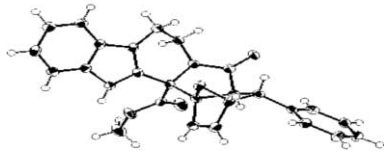
in EtOAc and washed with 1N HCl. The organic phase was then isolated, dried over Na_2SO_4, filtered and concentrated to give the crude product. Purification by silica gel flash chromatography or preparative TLC with EtOAC–Hex as eluent afforded the desired product. ^{1}H NMR (300 MHz, $CDCl_3$) for **8b**: δ 8.20 (s, 1H), 7.28 (d, 2 H, $J=8.2$ Hz), 7.05 (dd, 1H, $J=1.6$, $J=8.2$ Hz), 6.70 (d, 1H, $J=6.0$ Hz), 6.55 (dd, 1H, $J=1.9$, $J=6.0$ Hz), 6.45 (t, 1H, $J=4.9$ Hz), 5.15 (d, 1H, $J=1.7$ Hz), 4.60 (m, 1H), 3.90 (s, 3H), 3.25–2.70 (m, 7H), 2.42 (s, 3H), 1.72 (m, 1H), 0.85 (t, 6H).

Spectroscopic data for selected compounds. **Diol 9**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.15 (s, 1H), 7.50 (d, 1H, $J=1.6$ Hz), 7.40–7.10 (m, 7H), 4.55 (dd, 1H, $J=4.4$, $J=12.9$ Hz), 4.48 (d, 1H, $J=5.2$ Hz), 4.25 (d, 1H, $J=6.0$ Hz), 4.18 (d, 1H, $J=6.0$ Hz), 3.82 (s, 3H), 3.65 (t, 1H, $J=5.2$, $J=5.5$ Hz), 3.20 (d, 1H, $J=5.5$ Hz), 3.10 (m, 1H), 3.0–2.78 (m, 2H). **Compound 10**: ^{1}H NMR (300 MHz, CD_3OD): δ 7.45 (d, 1H, $J=2.2$ Hz), 7.35-7.15 (m, 6 H), 7.03 (m, 2H), 6.27 (dd, 1H, $J=1.6$, $J=6.0$ Hz), 5.03 (dd, 1H, $J=1.6$, $J=4.7$ Hz), 4.50 (dd, 1H, $J=5.2$, $J=13.2$ Hz), 4.35 (d, 1H, $J=12.1$ Hz), 4.12 (d, 1H, $J=12.1$ Hz), 3.65 (t, 1H, $J=4.1$, $J=4.4$ Hz), 3.25 (m, 2H), 2.78 (m, 2H). **Compound 11**: ^{1}H NMR (300 MHz, CD_3OD): δ 7.40 (d, 1H, $J=1.6$ Hz), 7.25–7.08 (m, 6 H), 6.97 (m, 2H), 6.15 (dd, 1H, $J=1.6$, $J=5.8$ Hz), 4.92 (dd, 1H, $J=1.6$, $J=4.7$ Hz), 4.07 (d, 1H, $J=11.0$ Hz), 3.90 (d, 1H, $J=11.0$ Hz), 3.40–3.12 (m, 4H), 2.95 (m, 2H), 2.50 (m, 2H). **Compound 12**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.47 (d, 1H, $J=1.6$ Hz), 7.25 (m, 4H), 7.10 (m, 3H), 6.57 (d, 1H, $J=5.8$ Hz), 6.20 (dd, 1H, $J=1.1$, $J=5.5$ Hz), 5.08 (dd, 1H, $J=1.1$, $J=4.4$ Hz), 3.90 (s, 3H), 3.45 (m, 2H), 3.30 (m, 2H), 3.0 (m, 2H), 2.60 (m, 2H). **Diol 13**: ^{1}H NMR (300 MHz, CD_3OD): δ 7.50–7.15 (m, 7H), 7.05 (dd, 1H, $J=2.2$, $J=8.5$ Hz), 4.32 (d, 1H, $J=5.5$ Hz), 4.25 (d, 1H, $J=6.1$ Hz), 3.92 (d, 1H, $J=6.3$ Hz), 3.78 (s, 3H), 3.42–3.18 (m, 4H), 3.12–2.80 (m, 3H), 2.58 (dd, 1H, $J=3.0$, $J=15.4$ Hz).

12. Crystals for cycloadduct **7a** were grown from EtOAc–acetone. We are pleased to acknowledge the contribution to this project provided by Dr. John C. Huffman and the X-ray crystallography laboratory of Indiana University.



7a



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