Enantioselective synthesis of 3-substituted tryptamines as core components of central nervous system drugs and indole natural products

Stephen Hanessian and Elia J.L. Stoffman

Abstract: Application of the MacMillan iminium ion Michael and Friedel–Crafts type reactions to γ-amino α,β-unsaturated butanals led to the corresponding β-substituted butanals in good yields and high enantioselectivities. The products could be useful intermediates in the synthesis of indole-based central nervous system (CNS) drugs and natural products.

Key words: iminium ion alkylation, indole natural products, 3-substituted indoles.

Résumé : L'utilisation d'ions iminium de MacMillan dans des réactions de type Michael ou Friedel–Crafts sur des γ-aminobutanals α,β-insaturés conduit à la formation des butanals β-substitués correspondants, avec de bons rendements et des énantiosélectivités élevés. Ces produits pourraient être des intermédiaires utiles dans la synthèse de produits naturels et de médicaments pour le système nerveux central (CNS) à base d'indole.

Mots-clés : alkylation d'un ion iminium, produits naturels à base d'indole, indoles avec substitution en position 3.

[Traduit par la Rédaction]

Introduction

The tryptamine moiety is found in a number of drugs as well as pharmacologically active alkaloids[1] that use L-tryptophan as a biosynthetic precursor.[2] Drug prototypes with demonstrated activity against a host of central nervous system (CNS)-related targets and containing various azacyclic rings attached to indoles are of interest. For example, NXN274 and naratriptan[3,4] are known to act on the serotonergic (5-hydroxytryptamine or 5-HT) receptors (Fig. 1).

Gelliusine E,[5] a member of the diindole methane family of alkaloids, has generated attention[6] owing to the novel biological profile of this class of symmetrical and nonsymmetrical bisindoles.

Results and discussion

In connection with a project aimed at exploiting a practical asymmetric synthesis of NXN274, we recently reported[3] the synthesis of an advanced intermediate, *S*-(–)-**1**, using MacMillan's iminium activation of α,β-unsaturated aldehydes as a means of stereocontrolled and enantioselective branching (Scheme 1).[7]

Although examples of Michael and Friedel–Crafts type additions to α,β-unsaturated aldehydes with alkyl and related substituents at the γ-position were known from the MacMillan group[7a,7e] and others,[8] we required an α,β-unsaturated butanal harbouring a functionalized amino group at the γ-carbon, such as **3**. We now report on the details of this approach toward the stereoselective synthesis of α-branched 3-substituted indoles (**4**), and its extension to other synthetically useful substrates.

The synthesis of the desired (*S*)-(–)-**1** is outlined in Scheme 2. The treatment of *N*-Boc, *N*-methyl acetaldehyde **5** with triethylphosphonoacetate under standard conditions followed by reduction with diisobutylaluminum hydride (DIBAL-H) led to allylic alcohol **6**, which was oxidized to the aldehyde **3** with the Dess–Martin periodinane reagent in an excellent yield. The activation of **3** with the (*R*,*R*)-MacMillan catalyst,[7a] followed by addition of 5-bromoindole, afforded the adduct **7** in a quantitative yield. Reduction to the alcohol **8** and mesylation or tosylation to **9**, followed by cleavage of the *N*-Boc group and treatment of the product with potassium carbonate in a mixture of tetrahydrofuran (THF) and dimethylformamide (DMF) as the solvent led to the target compound, (*S*)-(–)-**1**, in an excellent yield. The absolute configuration was confirmed by single crystal X-ray analysis (see ref. 3 of the Supplementary data), and stereochemical purity (88% enantiomeric excess (ee)) was established by chiral HPLC analysis.

The suitability of **3** as a Michael acceptor in the MacMillan organocatalytic addition of 5-bromoindole to give β-branched aldehydes such as **7** with high enantioselectivity led us to explore the same reactions with other N substituents.

The results shown in Table 1 indicate that a variety of N substituents can be used in the original reaction with excellent enantioselectivities, which did not seem to vary significantly with less sterically bulky protecting groups on nitrogen (Table 1, entry 3) or when groups with a stronger

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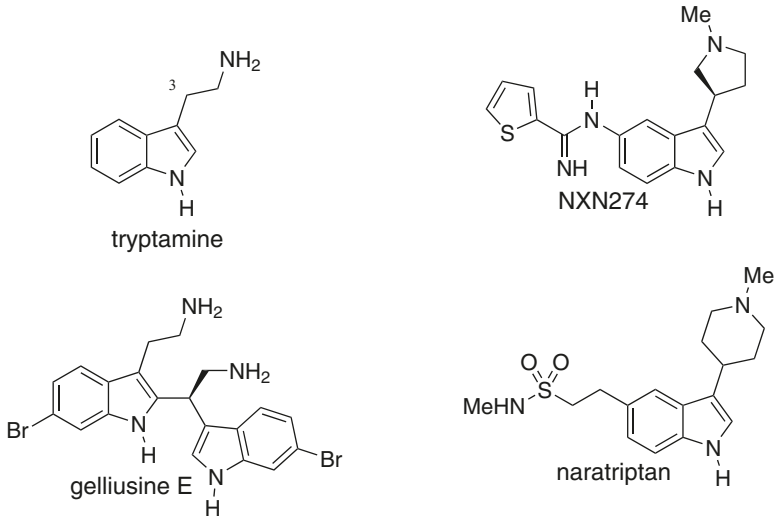
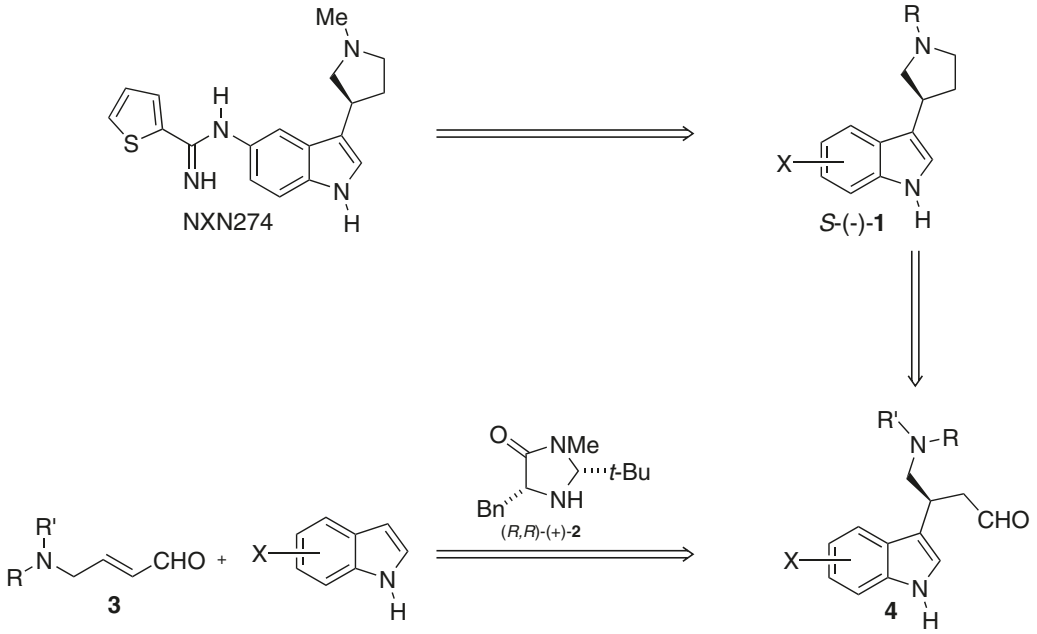
Fig. 1. Examples of 3-substituted tryptamines as drugs or natural products.



Scheme 1. Retrosynthetic analysis of NXN274.



electron-withdrawing capability were introduced (Table 1, entry 2). However, when the bulkier bis-protected substrates were used, longer reaction times were necessary (Table 1, entries 4 and 5).

The synthesis of the bis-protected aldehyde **15** (Table 1, entries 4 and 5) proceeded smoothly through a cross-metathesis approach (Scheme 3). Thus, anisaldehyde (**10**) was reductively aminated with allylamine (**11**) to give *N*-allyl-4-methoxybenzylamine (**12**), and this was protected as the *tert*-butylcarbamate **13**. Cross metathesis with methyl acrylate in the presence of the Grubbs II catalyst gave the methyl ester **14**, which was reduced to the corresponding alcohol before oxidation by the Parikh–Doering method to the bis-protected aminoaldehyde **15**.

We then turned our attention to α,β-unsaturated aldehydes containing γ- and δ-amino groups protected as the *tert*-butylcarbamates (Scheme 4).

The use of aldehyde **16a**[9] under the conditions established in Table 1 (vide supra) led to transformation of the aldehyde to *N*-Boc–pyrrole, without incorporation of the indole moiety. However, the homologated aldehyde **16b**[10] underwent smooth conversion to the cyclized *N*-Boc enamine **17**, which could be converted to the *O*-methyl hemiaminal **18** under acid catalysis. The latter could be converted to the achiral naratriptan precursor (**19**) under conditions reported by Leonard and Woerpel[11] (BF_3–OEt_2, Et_3SiH), or by hydrogenation over Rh catalyst in the presence of AcOH.[12] In the absence of acetic acid, neither *O*-methyl hemiaminal **18**

Scheme 2. Synthesis of *S*-(–)-**1**. Reagents and conditions: (*a*) (*i*) triethylphosphonoacetate, NaH, THF, room temperature (rt), 30 min; (*ii*) DIBAL-H, THF, –78 °C, 30 min, 54% (two steps); (*b*) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 89%; (*c*) 5-bromoindole, (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one, trifluoroacetic acid (TFA), *i*-PrOH, CH_2Cl_2, –78 °C, 36 h, quant.; (*d*) $NaBH_4$, MeOH, rt, 2 h; (*e*) R = Me, MsCl, CH_2Cl_2, Et_3N, 0 °C to rt, 16 h, 80% (2 steps); R = *p*-tolyl, TsCl, CH_2Cl_2, Et_3N, 0 °C to rt, 16 h, 70% (two steps); (*f*) (*i*) HCl, 1,4-dioxane, 0 °C to rt, 1.5 h; (*ii*) K_2CO_3, THF–DMF, rt, 24 h, quant. for both sulfonates.

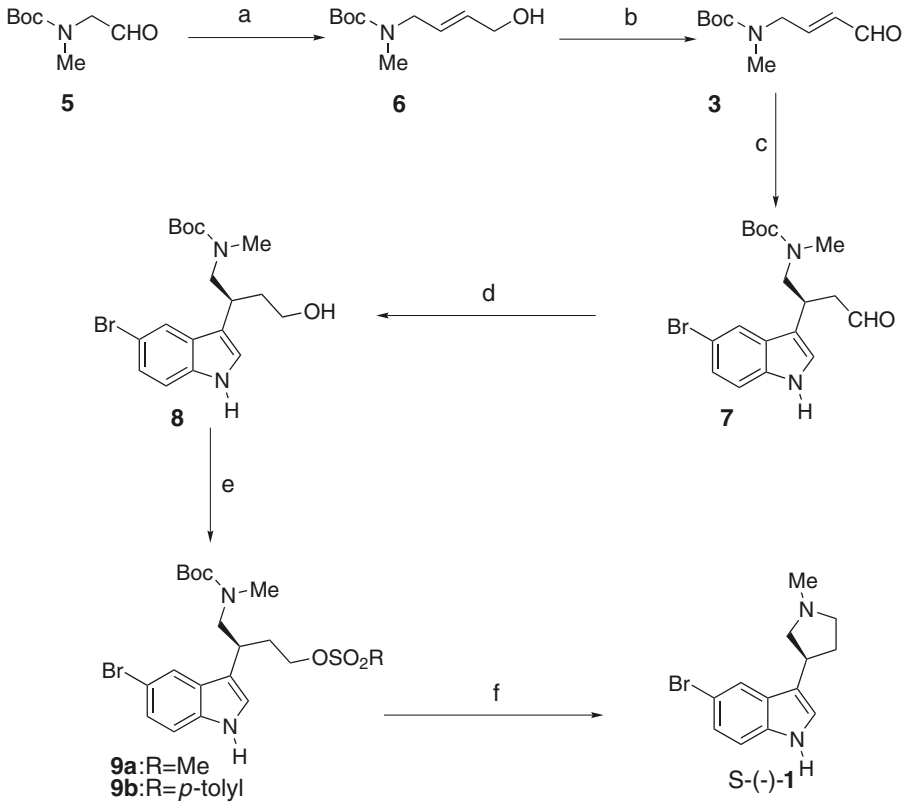
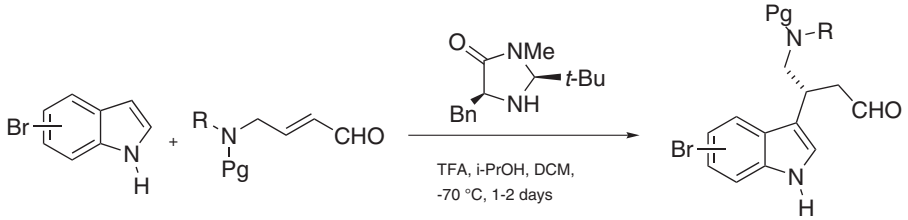


Table 1. Organocatalytic MacMillan indole alkylation using nitrogen-containing aldehydes.



Entry	Pg	R	Br position	Yield (%)[a]	ee (%)[b]	Time (days)
1	Boc	Me	5	Quant.	82	1
2	Bus	Me	5	89[c]	92	1
3	COOMe	Me	5	97	91	1
4	Boc	PMB	5	80	88	2
5	Boc	PMB	6	65 (83)[d]	81	2

Note: PMB, *p*-methoxybenzyl ether; quant., quantitative.

[a]Pure isolated yield unless otherwise indicated.

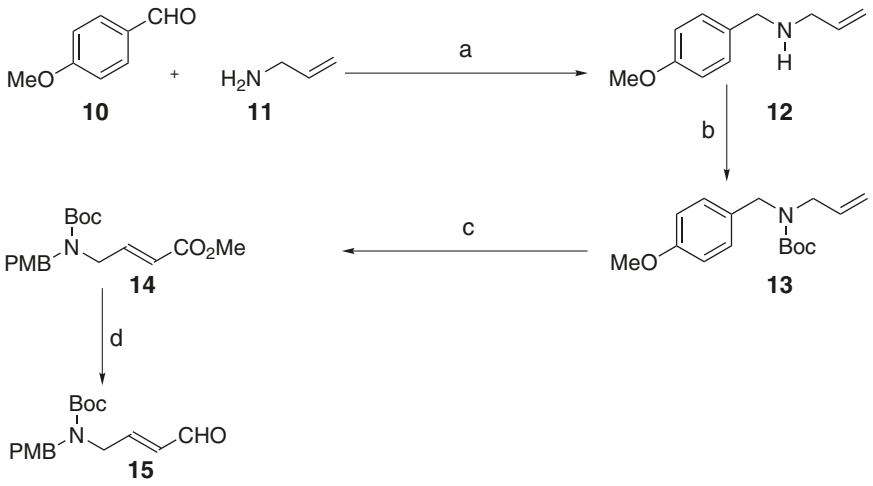
[b]Based on chiral HPLC analysis of the corresponding alcohols obtained by $NaBH_4$ reduction. The opposite enantiomer was obtained by running the reaction using the enantiomeric MacMillan catalyst.

[c]Pure isolated material (61%) and 28% in a mixture with starting aldehyde as determined by ^{1}H NMR.

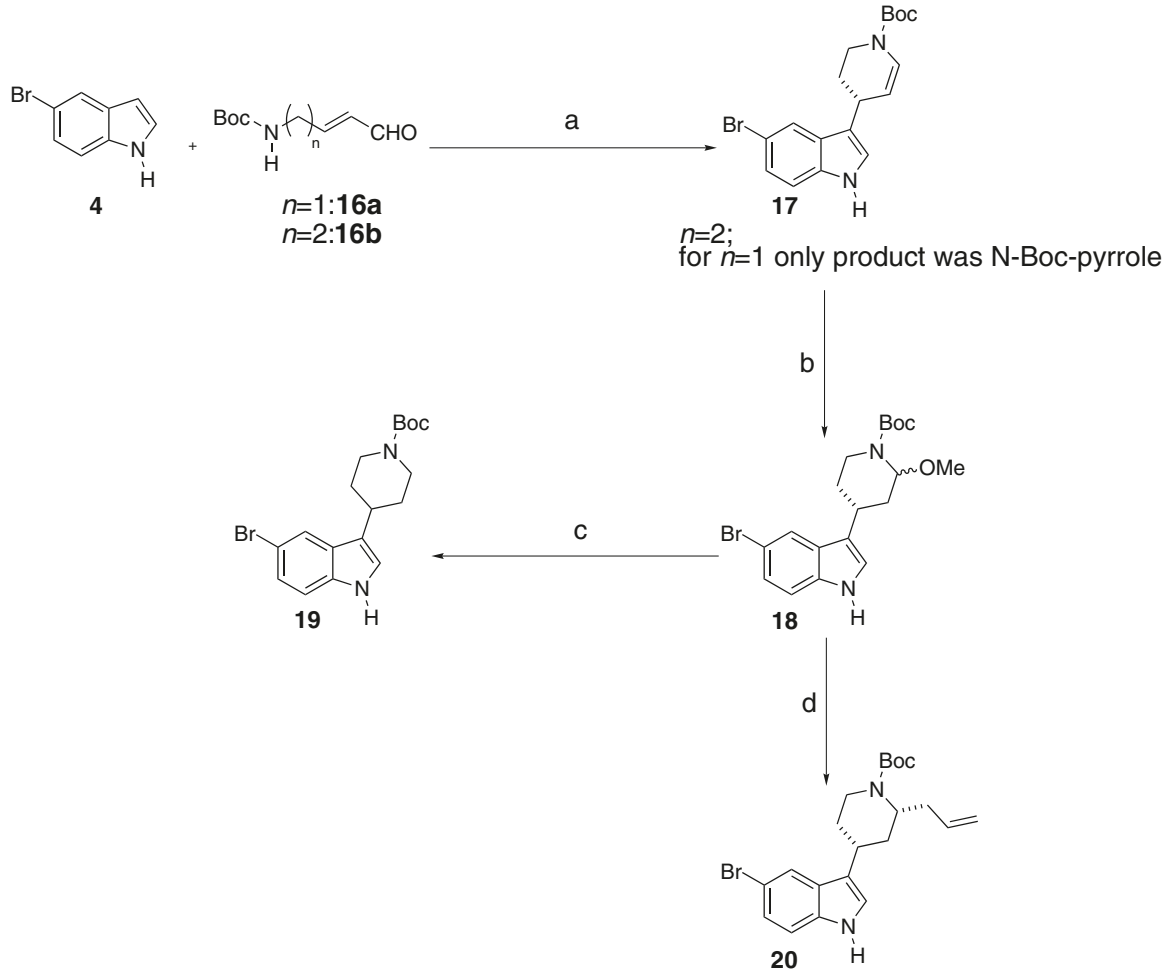
[d]Corrected for recovered 6-bromoindole.

nor enamine **17** were reduced by catalytic hydrogenation using either Rh-on-carbon or Crabtree's catalyst[13] at 8 atm (1 atm = 101.325 kPa) of hydrogen for 24 h. The treatment of **18** with allyltrimethylsilane in the presence of BF_3–OEt_2[11] afforded the 2-allyl naratripan analog **20**, an asymmetric naratriptan analog.

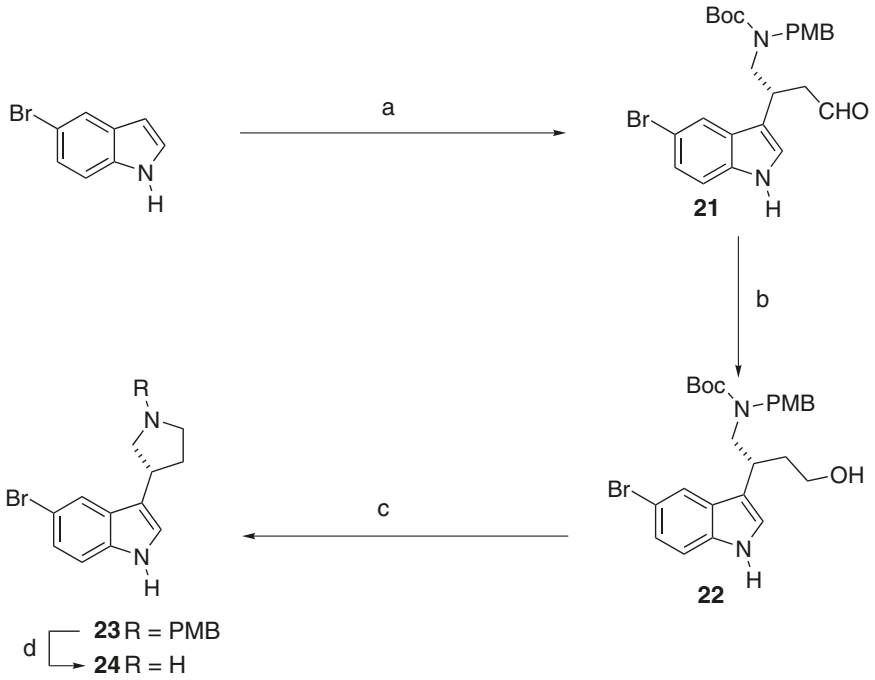
Scheme 3. Synthesis of bis-protected aminoaldehyde **15**. Reagents and conditions: (*a*) (*i*) $MgSO_4$, dichloromethane (DCM); (*ii*) $NaBH_4$, MeOH, 4 Å molecular sieves, 54% (two steps); (*b*) Boc_2O, THF, 50 °C, 91%; (*c*) methyl acrylate, Grubbs II, DCM, 52%; (*d*) (*i*) DIBAL-H, PhMe, –78 °C, 52%; (*ii*) SO_3-pyridine, triethylamine (TEA), dimethyl sulfoxide (DMSO), DCM, 74%.



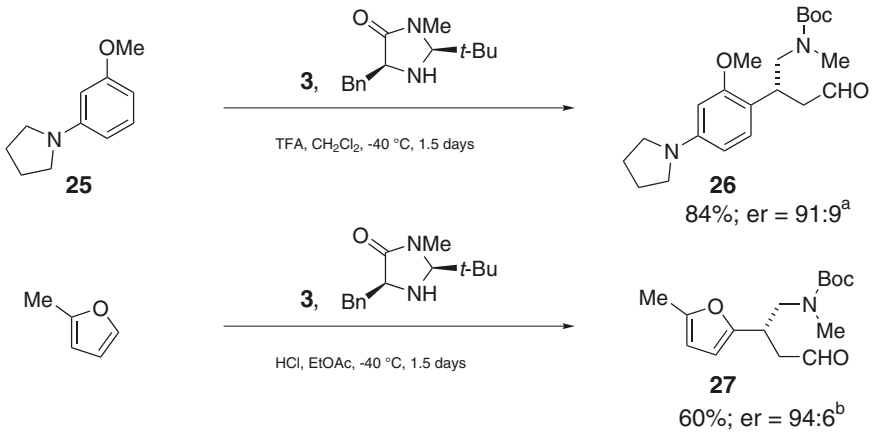
Scheme 4. Synthesis of naratriptan analogs. Reagents and conditions: (*a*) (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methylimidazolidin-4-one, TFA, *i*-PrOH, CH_2Cl_2, –70 °C, 1 day; (*b*) TsOH–H_2O, MeOH, 70% (two steps); (*c*) H_2 (8 atm; 1 atm = 101.325 kPa), Rh-C, AcOH, 62% or BF_3–OEt_2, Et_3SiH, 58%; (*d*) BF_3–OEt_2, allyltrimethylsilane, 23%.



Scheme 5. The use of bis-protected aldehyde **15** to generate a substrate suitable for indole-3-pyrrolidine synthesis. Reagents and conditions: (*a*) **15**, (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one, TFA, *i*-PrOH, CH_2Cl_2, –70 °C, 1.5 day; (*b*) $NaBH_4$, MeOH, 84%; (*c*) (*i*) MsCl, TEA, 70%; (*ii*) HCl, EtOAc; (*iii*) K_2CO_3, DMF, 85%; (*d*) (*i*) α-chloroethylchloroformate, CH_2Cl_2; (*ii*) MeOH, reflux, 45%.



Scheme 6. Synthesis of enantioenriched phenethylamines and 2-ethylamino furans.



To circumvent the acid-induced decomposition of aldehyde **16a** to *N*-Boc–pyrrole, we investigated an alternative approach (Scheme 5) now utilizing the enantiomeric MacMillan catalyst *ent*-(–)-(**2**).

Starting from **21** (Table 1, entry 5), we first reduced the aldehyde to the primary alcohol **22**. Mesylation of alcohol **22** and removal of the Boc group resulted in a spontaneous cyclization to the pyrrolidine **23**. Removal of the PMB protecting group was easily accomplished using α-chloroethylchloroformate[14] to furnish **24**, the des-*N*-methyl enantiomer of *S*-(–)-**1**.

Paras and MacMillan[7e] reported Friedel–Crafts type conjugate additions of electron-rich aromatics and heterocyclics to α,β-unsaturated aldehydes. The extension of this reaction to 4-*N*-Boc-*N*-methyl butanal provided access to enantioenriched 3-substituted butanals. Thus, the treatment of **3** with 3-pyrrolidino anisole in the presence of the MacMillan (*S*,*S*) imidazolinone catalyst *ent*-**2** in methylene chloride at –40 °C led to the phenethylamine derivative **26** in an 84% yield and 91:9 enantiomeric ratio (Scheme 6). A similar reaction with 2-methylfuran, albeit using EtOAc as the solvent, led to the substituted 2-methylfuran derivative **27** in a 60% yield and 94:6 enantiomeric ratio.

Conclusion

Butanals containing N substituents at the γ-carbon atom are excellent substrates for Michael and Friedel–Crafts type conjugate additions of indoles and electron-rich aromatics,

respectively, affording suitably functionalized adducts in high diastereomeric ratios. The extension of MacMillan's organocatalytic indole alkylation to nitrogen-containing aldehydes was realized and has found application in our concise synthesis of *S*-(–)-**1**, a late-stage intermediate in the synthesis of the dual action migraine drug prototype NXN274. We expect that this methodology will also find applications in alkaloid synthesis and in the synthesis of other indole-containing compounds of medicinal interest.

Experimental

General

The *J* values are spacings measured directly from the spectrum. Dry solvents were purified using a sodium dodecyl sulfate (SDS) system or purchased as such (Sigma-Aldrich). Column sizes are quoted as (width × height). Melting points were measured on a Büchi melting point B-540 apparatus and are uncorrected. Optical rotations were recorded on a PerkinElmer model 343 polarimeter at ambient temperature.

N-*Allyl*-N-*4-methoxybenzylamine (12)*

Anisaldehyde (0.44 mL, 3.6 mmol), allylamine (0.29 mL, 1.1 equiv), and $MgSO_4$ (0.5 g) in CH_2Cl_2 (5.4 mL) were mixed and the solution was stirred for 3 h (TLC control) and then the mixture was filtered and the filtrate solution was concentrated in vacuo.[15]

The crude aldimine was then taken up in MeOH (6 mL) and 4 Å molecular sieves (1 g), followed by $NaBH_4$ (0.13 g, 3.4 mmol) were added with stirring. The flask was flushed with Ar and stirring was continued for 2 h, then the mixture was diluted with Et_2O (25 mL) and extracted twice with 10% HCl (10 mL each). The combined acidic extracts were basified with 3 N NaOH and extracted twice with Et_2O (30 mL total). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to afford **12** (0.34 g, 54%), which had data identical to that previously reported.[15]

N-tert-*Butylcarbonyl*-N-*allyl*-N-*4-methoxybenzylamine (13)*

Boc_2O (0.49 mL, 1.1 equiv) was added to a stirred solution of **12** (0.3421 g, 1.930 mmol) in THF (6 mL) under Ar and the mixture was stirred at rt overnight. Removal of the volatiles in vacuo afforded **13** (0.4865 g, 91%), having spectral data identical to that previously reported.[16]

*4-[*tert*-Butoxycarbonyl-(4-methoxy-benzyl)amino]but-2-enoic acid methyl ester (14)*

The Grubbs II catalyst (34 mg, 0.040 mmol) was added to a stirred solution of **13** (0.4159 g, 1.500 mmol) and methyl acrylate (5.4 mL) in CH_2Cl_2 (6.6 mL). The flask was flushed with Ar and stirring was continued overnight. The mixture was filtered through a plug of SiO_2 (2 cm × 2 cm) using 5% EtOAc–hexanes to wash the plug and then the volatiles were removed in vacuo. Flash chromatography over SiO_2 (1.5 cm × 25 cm) using 5% EtOAc–hexanes afforded **14** (0.2594 g, 52%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (br s, 2H), 6.85 (d, J = 8.44 Hz, 2H), 6.82–6.86 (m overlapping with previous, 1H), 5.81–5.85 (m, 1H), 4.36 (br s, 2H), 3.94 (br s, 1H), 3.79 (s, 3H), 7.74–3.80 (m overlapping, 1H), 3.74 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.4, 46.6, 49.2, 51.6, 55.3, 80.3, 114.0, 121.6, 128.8, 129.3, 129.6, 144.1, 155.4, 159.0, 166.5 (peaks at 128.8 and 129.3 appear to arise from a single C, but doubled owing to Boc carbamate). Exact mass *m/z* calcd for $C_{18}H_{25}NNaO_5$: 358.16249 (M + Na); found: 358.16086.

(4-Methoxy-benzyl)-(4-oxo-but-2-enyl)carbamic acid tert-*butyl ester (15)*

DIBAL-H (1.6 mL, 1 mol/L in hexanes, 1.6 mmol) was added via syringe to a stirred and cooled (–78 °C) solution of **14** (0.2426 g, 0.7432 mmol) in PhMe (2.2 mL) under Ar. After 30 min, the cooling bath was removed and the mixture was quenched by the addition of saturated aqueous Rochelle's salt (1.5 mL), diluted with Et_2O (20 mL), and washed once with saturated aqueous Rochelle's salt (5 mL). The organic layer was allowed to stand overnight and the next day the gel that formed was filtered through Celite. Filtration of the residue through a pad of SiO_2 (2 cm × 2 cm) using 40% EtOAc–hexanes afforded the allylic alcohol (0.1152 g, 52%), which was oxidized using the Parikh–Doering method.

SO_3–pyridine (0.12 g, 0.75 mmol) was added in one portion to a stirred and cooled (0 °C) solution of allylic alcohol (from the DIBAL reduction; 0.1152 g, 0.3748 mmol), Et_3N (0.10 mmol), and DMSO (0.22 mL) in CH_2Cl_2 (3 mL). Stirring was continued for 10 min before the ice bath was removed and stirring was then continued for a further 2 h. The mixture was then diluted with CH_2Cl_2 (5 mL) and the mixture was washed once with water (6 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over SiO_2 (1.5 cm × 20 cm) using 20% EtOAc–hexanes afforded **15** (85.1 mg, 74%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.52 (d, J = 7.8 Hz, 1H), 7.14 (br s, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.67 (br s, 1H), 6.08 (dd, J = 7.4, 15.4 Hz, 1H), 4.36 (br s, 2H), 3.97–4.05 (m, 2H), 3.79 (s, 3H), 1.48 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.4, 47.1, 49.7 and 50.1 (doubled peak), 55.3, 80.6, 114.0, 128.8, 129.5, 132.5, 152.9, 155.3, 159.1, 193.2. Exact mass *m/z* calcd for $C_{17}H_{23}NNaO_4$: 328.15193 (M + Na); found: 328.15163.

*4-(5-Bromo-1*H*-indol-3-yl)-3,4-dihydro-2*H*-pyridine-1-carboxylic acid* tert-*butyl ester (17)*

A flask was charged with MacMillan's catalyst (2*R*,5*R*)-5-benzyl-2-*tert*-butyl-3-methyl-imidaolidin-4-one (6.8 mg, 0.13 mmol) and then TFA (0.04 mL, 0.03 mmol) was introduced via syringe. The flask was flushed with Ar, cooled to –70 °C (cooling machine), and **16b** (0.4012 g, 2.014 mmol) in CH_2Cl_2 (1.3 mL) and *i*-PrOH (0.2 mL) were introduced via syringe. The mixture was stirred for 5 min, then 5-bromoindole (0.13 g, 0.67 mmol) was added in one portion. The flask was reflushed with Ar and stirring was continued for 1.5 days, at which point condensing atmospheric water had caused the acetone cooling bath to reach –65 °C. The mixture was removed from the cooling bath, diluted with CH_2Cl_2 (10 mL), washed once with water, and dried ($MgSO_4$). Flash chromatography of the residue over SiO_2 (1.5 cm × 20 cm) using 25% EtOAc–hexanes afforded **17** (66 mg), which was converted directly to **18** (see the following section). An analytical sample had $[\alpha]_D^{25}$ +14.6° (*c* 0.77, $CHCl_3$). FT-IR (film cast, cm^{-1}): 3431, 1678, 1648, 1458, 1406, 1367, 1299, 1235, 1164, 1120, 987. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (br s, 1H), 7.76 (s, 1H), 7.29 (d, J = 1.8 Hz, 1H), 7.24 (dd, J = 8.2, 0.4 Hz, 1H), 6.91–7.07 (m, 1H), 6.97 (d, J = 2.1 Hz, 1H), 4.97–5.09 (m, 1H), 3.66–3.73 (overlapping m, 2H), 3.42–3.50

(m, 1H), 2.18 and 1.96 (two br s, 1H), 1.61 and 1.50 (two s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 28.2, 28.6, 28.9, 39.0, 40.0, 80.7, 107.1, 107.5, 112.4, 112.5, 119.4, 121.3, 123.0, 123.3, 124.8, 125.5, 125.8, 127.8, 128.2, 135.1, 152.1, 152.7. Exact mass *m/z* calcd for $C_{18}H_{21}BrN_2NaO_2$: 399.06786 (M + Na); found: 399.06807.

4-(5-Bromo-1*H*-indol-3-yl)-2-methoxypiperidine-1-carboxylic acid* tert-*butyl ester (18)

TsOH–H_2O (2 mg, 0.01 mmol) was added to a stirred solution of **17** (66 mg, assumed to be 0.67 mmol from the previous transformation) in MeOH (2 mL). The flask was flushed with Ar and stirring was continued for 1 day. Evaporation of the solvent and flash chromatography over SiO_2 (1.5 cm × 20 cm) using 20% EtOAc–hexanes afforded **18** as a mixture of diasteromers (39.4 mg, 72%).

4-(5-Bromo-1*H*-indol-3-yl)-piperidine-1-carboxylic acid* tert-*butyl ester (19)

Et_3SiH (0.3 mL, 5% v/v in CH_2Cl_2, 0.1 mmol) followed by BF_3-OEt_2 (0.14 mL, 5% v/v in CH_2Cl_2, 0.057 mmol) were added via syringe to a stirred and cooled (–78 °C) solution of **18** (9.7 mg, 0.024 mmol) in CH_2Cl_2 (0.5 mL) under Ar. The mixture was stirred for 1 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL). The aqueous phase was extracted once with CH_2Cl_2 (5 mL) and dried ($MgSO_4$). Flash chromatography over SiO_2 (0.5 cm × 10 cm) using 20% EtOAc–hexanes afforded **19** (5.2 mg, 58%); mp 199–200 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (br s, 1H), 7.72 (m, 1H), 7.19–7.26 (overlapping m, 2H), 6.93–6.94 (m, 1H), 4.21 (ddd, *J* = 13.3, 2.1, 2.1 Hz, 2H), 2.84–2.95 (m overlapping with next, 1H), 2.85 (ddd, *J* = 13.0, 13.0, 2.4 Hz, 1H), 2.02–1.96 (m, 2H), 1.54–1.67 (m, 2H), 1.46 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.4, 22.0, 39.4, 123.9, 126.4, 127.0, 128.1, 128.2, 129.3, 142.1, 143.9, 155.5 (signals from Boc *t*-Bu did not appear). Exact mass *m/z* calcd for $C_{18}H_{23}BrN_2NaO_2$: 401.08351 (M + Na); found: 401.08548. X-ray crystallographic data are given in Appendix 1 in the Supplementary data. Compounds **18** and **19** had the same R_f by TLC; however, **19** stained purple with anisaldehyde.

(*R*)-2-Allyl-(5-bromo-1*H*-indol-3-yl)piperidine-1-carboxylic acid* tert-*butyl ester (20)

Allyltrimethylsilane (0.02 mL, 0.13 mmol) followed by BF_3-OEt_2 (0.22 mL, 5% v/v in CH_2Cl_2, 0.089 mmol) were added via syringe to a stirred and cooled (–78 °C) solution of **18** (16.1 mg, 0.039 mmol) in CH_2Cl_2 (0.5 mL) under Ar. The mixture was stirred for 1 h, then quenched by the addition of saturated aqueous $NaHCO_3$ (0.5 mL). The aqueous phase was extracted once with CH_2Cl_2 (5 mL) and dried ($MgSO_4$). Flash chromatography over SiO_2 (0.5 cm × 10 cm) using 20% EtOAc–hexanes afforded **20** (3.7 mg, 23%). Compounds **18** and **20** had the same R_f by TLC; however, **20** stained a different colour using anisaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (br s, 1H), 7.71 (m, 1H), 7.19–7.27 (overlapping m, 2H), 6.92–6.93 (m, 1H), 5.79 (dddd, *J* = 17.1, 10.1, 7.2, 7.2 Hz, 1H), 5.12 (dddd, *J* = 18.4, 1.9, 1.9, 1.9 Hz), 5.05–5.09 (m, 1H), 4.42 (app br s, 1H), 4.13 (app br s, 1H), 2.95–3.20 (m, 1H), 2.36–2.58 (m, 1H), 1.71 (ddd, *J* = 13.3, 13.3, 5.5 Hz, 1H), 1.41–1.50 (overlapping m, 2H), 1.46 (s, 9H), 0.81–0.95 (m, 1H). Exact mass *m/z* calcd for $C_{21}H_{27}BrN_2NaO_2$: 441.11481 (M + Na); found: 441.11557.

Supplementary data

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/cjc-2012-0221. CCDC 898223 contains the X-ray data in CIF format for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/products/csd/request. (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 33603; or e-mail: deposit@ccdc.cam.ac.uk.)

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