Expedient and Stereoselective Access to Diverse Alkaloid-like Scaffolds via an Oxidation/Double-Mannich Reaction Sequence

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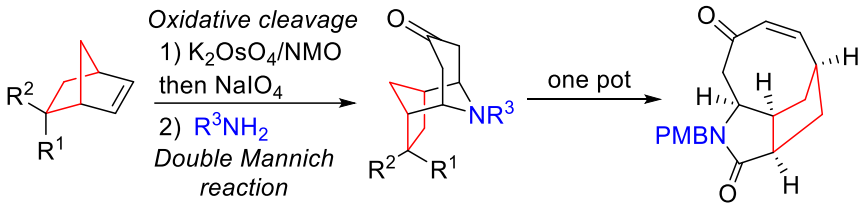
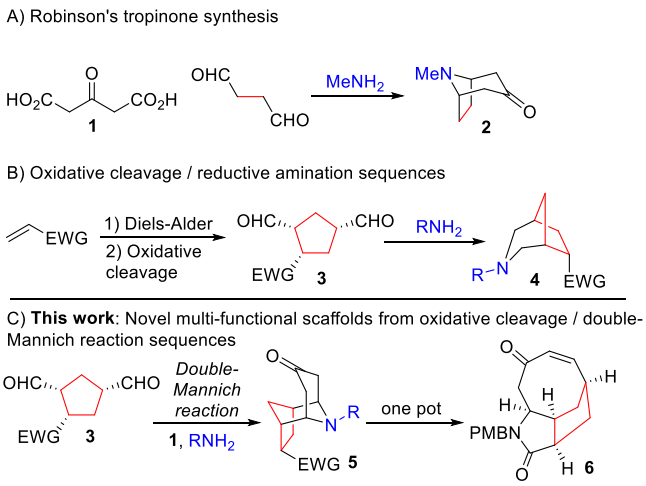


ABSTRACT: Sequential oxidative cleavage and double-Mannich reactions enable the stereoselective conversion of simple norbornenes into complex alkaloid-like structures. The products undergo a wide range of derivatization reactions, including a regioselective enol triflate formation/cross-coupling sequences and highly efficient conversion to an unusual tricyclic-8,5,5 fused lactam. Overall, the process represents a formal 1-atom aza-ring expansion with concomitant bridging annulation, making it of interest for the broader derivatization of alkene feedstocks.

Access to novel small molecule scaffolds is of great importance to the field of medicinal chemistry,[1-3] and recently there has been particular focus on forming scaffolds with high three-dimensionality due to such compounds' improved success within clinical trials.[3,4] Rigid three-dimensional scaffolds are of particular interest, with bridged bi- and poly-cyclic architectures being of particular importance due to their frequently potent bioactivity[6,7] and associated current synthetic interest.[8-12] Ideally, such systems would also offer the ability to perform orthogonal functionalization so as to enable facile library synthesis.[13]

Natural products have historically proved a useful starting point for drug discovery, with up to 75% of drugs being derived from or inspired by molecules originating in nature.[14] The alkaloid family in particular has proved an excellent source of CNS active compounds, which is an area of medicinal chemistry that continues to offer significant challenges.[15-17] However, synthetic access to alkaloid structures is frequently limited by complex syntheses, with each route typically offering access to only a single ring system. Broader access to alkaloid-like chemical space is therefore highly desirable,[18,19] and indeed access to such analogues has seen considerable recent interest.[20-24] Biomimetic syntheses offer attractive approaches to such systems,[25,26] with arguably the first example of this being Robinson's synthesis of tropinone **2** (Scheme 1a), which achieved this via a one-step double-Mannich reaction.[27,28] However, such an approach has yet to be extended more broadly, despite potentially enabling a general conversion of easily accessed dialdehydes into complex natural product-like scaffolds. We considered that stereochemically rich 1,4-dialdehydes of type **3**, which are readily available from Diels-Alder cycloaddition/oxidative cleavage sequences, might be attractive substrates in this respect. Indeed, such systems have seen use in reductive amination-based diversification to form systems of type **4** (Scheme 1b);[29,30] however, their extension to double-Mannich reactions remains essentially unexplored.[31] Overall, such an approach would represent a one atom ring expansion of simple alkenes, forming systems that appear attractive as scaffolds for derivatization into compound libraries.

Scheme 1. Previous and current access to three-dimensional amine scaffolds from dialdehyde building blocks.



In contrast to reductive amination reactions involving dialdehyde **3**, a double Mannich reaction would necessarily generate far greater stereochemical complexity, and stereocontrol of this process was therefore a key concern. Our starting point was thus *tert*-butyl system **9a**, where we envisaged that the bulky ester would potentially offer stereocontrol in the key enolate addition

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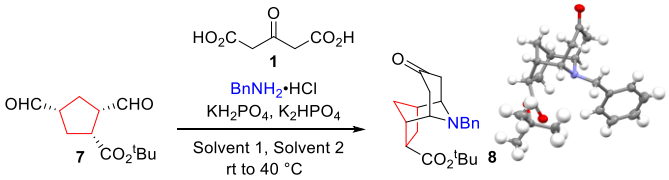
step, thereby relaying the stereochemical information from the initial norbornene-forming Diels-Alder cycloaddition.

Oxidative cleavage was initially attempted via both one-step and two-step approaches; however, both one-step approaches using either ozone or OsO_4 in the presence of sodium periodate led to considerable loss of mass. Gratifyingly however, a two-step approach proved considerably more successful, in which intermediate diol was directly reacted with sodium periodate to form dialdehyde **7**. Optimization of conditions permitted Os(VI) pre-catalyst loadings as low as 0.3 mol% with quantitative yield over two steps. The resulting aldehyde proved to be highly sensitive and was thus used directly in the subsequent double-Mannich reaction step without purification.

While conditions for performing double Mannich reactions on succinaldehyde to form tropinone systems are well developed,[27] such reactions are typically performed under aqueous conditions which limits the solubility of hydrophobic species such as **7**. We initially focused on the use of benzylamine as the amine partner (Table 1), which showed that while such reactions can be performed with water as sole solvent (entry 1), increasing the reaction scale became challenging due to a significant lack of homogeneity. We therefore undertook the small screen of organic co-solvents as shown in Table 1. Surprisingly, yields for all systems were high and all reactions proceeded with high levels of stereoselectivity. However, several systems were far from homogenous, leading to considerable issues with stirring. Moving to water-dioxane systems reduced this issue, resulting in somewhat increased yields and far greater ability to perform reaction scale up. In all cases essentially a single diastereomer of product **8** was observed, suggesting that the bulky *tert*-butyl ester offered sufficient steric control. The stereochemistry of the product was confirmed by single crystal XRD, demonstrating that attack of the acetone-derived enolate on the intermediate iminium ion occurs from the opposite face to the bulk ester moiety.

Table 1. Optimisation of the double-Mannich reaction.

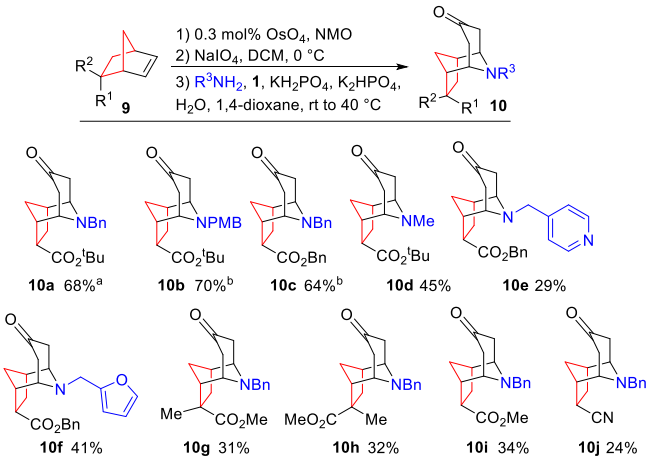


Entry	Solvent 1	Solvent 2	Yield /%[a,b]
1	H_2O	None	72[c]
2	H_2O	THF	65[c]
3	THF	None	61[d]
4	H_2O	1,4-dioxane	68
5	H_2O	MeCN	69[c]
6	H_2O	DMF	69

[a] All yields are given over three steps. [b] Reactions were performed on a 1.3 mmol scale at a concentration of 0.1 M. [c] Reaction scale limited by precipitation of organic materials. [d] Scale limited by poor solubility of inorganic bases.

With optimal reaction conditions identified we next undertook a study of the substrate scope of the reaction. As shown in Scheme 3, the reaction tolerated variation of both norbornene and amine components. Use of simple methyl esters as activating groups in the initial Diels-Alder reaction led to lower yields, in part because of the formation of more complex reaction mixtures, together with their greater water solubility reducing the product isolation in the intermediate oxidation steps. Importantly, both *endo* and *exo* norbornene stereoisomers gave clean conversion to opposite product diastereomers. Further, the inclusion of heterocyclic moieties were found to be well tolerated across all three steps as shown by the formation of pyridine **10d** and furan **10f**. Substituted benzylamines could also be employed as shown by the formation of PMB system **10b**, and simple alkyl amines also proved viable substrates as shown in the formation of methyl amine system **10i**. Use of other activating moieties also proved possible albeit with a decrease in yield, with nitrile **10j** being formed in low yield, again relating to low mass recoveries within the oxidation sequence. Given the low cost of all starting materials and the intended use of the products as scaffolds for diversification, reaction scale-up was also explored. Gratifyingly, multi-gram scale synthesis was easily achieved in three cases, with products being obtained in near identical yield to the smaller scale reactions.

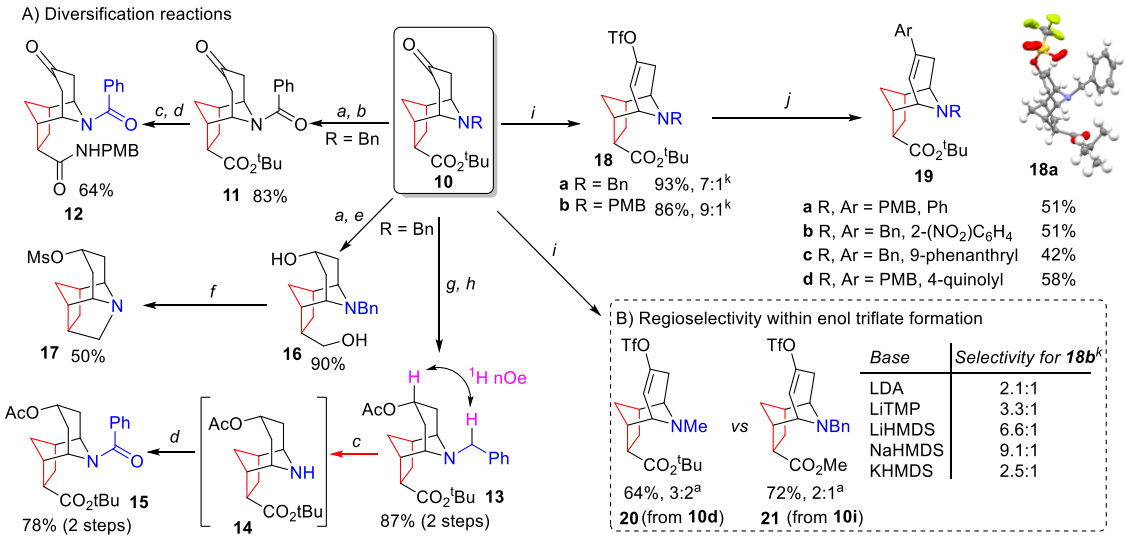
Scheme 2. Scope of the oxidative cleavage/double Mannich reaction sequence.



All yields are isolated yields over three steps. [a] Performed on a 5 g scale. [b] Performed on a 3 g scale.

We next explored derivatization of the products. All such compounds represent attractive scaffolds for medicinal chemistry, possessing significant structural rigidity, three-dimensionality and appropriate functionality to enable broad library synthesis. As shown in Scheme 3, deprotection of the *N*-benzyl moiety of **10a** is easily achieved, enabling efficient amide formation around the resulting secondary amine to form system **11**. The ester moiety was then easily functionalised, with a one-pot acid-promoted deprotection/amidation sequence forming diamide **12** in good yield. Further, the ketone moiety of **10b** was stereoselectively reduced with $NaBH_4$, with the incoming hydride being delivered from the same face as the amine. The resulting alcohol was then efficiently acetylated, providing a single diastereomer of compound **13**. The resulting compound underwent clean debenzylation via hydrogenolysis to form secondary amine **14**, which enabled direct access to the free amino acid via *tert*-butyl ester deprotection using TFA, or conversion to the corresponding amide as shown through the formation of **15**.

Scheme 3. A) Derivatization of scaffold 10 and B) Regioselectivity within enol triflate formation



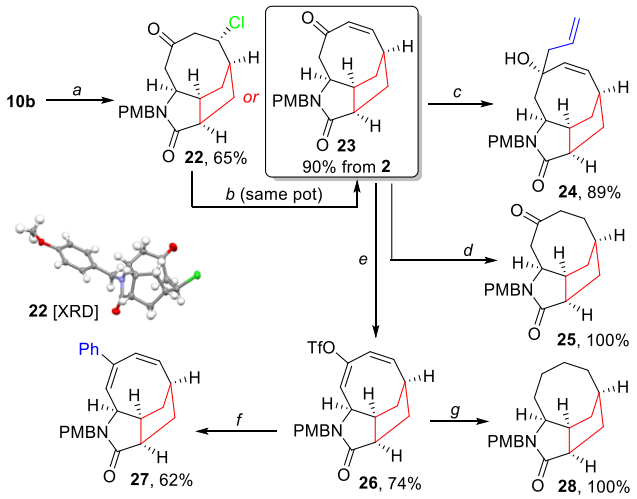
a) Pd/C (10%), HCO_2NH_4, MeOH, 60 °C. b) PhCOCl, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C to rt; c) TFA, CH_2Cl_2, 0 °C *then* oxalyl chloride, CH_2Cl_2, 0 °C; d) $PMBNH_2$, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C to rt; e) $LiAlH_4$, THF, 0 °C to 60 °C; f) MsCl, $^iPr_2NEt$, CH_2Cl_2; g) $NaBH_4$, MeOH, H_2O, rt; h) Ac_2O, $^iPr_2NEt$, DMAP, CH_2Cl_2, 0 °C to rt; i) NaHMDS, THF, -78 °C, *then* $PhNTf_2$, to rt; j) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, 1,4-dioxane, 85 °C; k) determined by ^1H NMR analysis of the crude reaction product.

Combined, these sequences demonstrate the potential of scaffold **10** to reliably form 3D compound libraries via standard amide formation processes, as well as its potential to be incorporated into peptides as an unnatural amino acid residue.

Having explored amidations and esterifications, we next investigated whether cyclisation of the amine and ester moieties, which are clearly close in space, was possible. Gratifyingly, reduction of both carbonyl functionalities was achieved efficiently with $LiAlH_4$, following which direct hydrogenolysis and double mesylation of the crude diol allowed cyclisation to tetracycle **17** which retains a single unreacted mesylate moiety. The ketone moiety also appeared to offer the opportunity to access standard Pd-catalysed diversification routes[32-34] via conversion to the corresponding enol triflate. Pleasingly, despite concerns regarding the formation of regioisomeric mixtures during enol triflate formation, we observed some selectivity in initial reactions. This was optimized though variation of base (Scheme 3b), with NaHMDS proving optimal, giving access to both *N*-benzyl and *N*-PMB systems **18** with good levels of regiocontrol. This selectivity is somewhat surprising given the remote position of the ester moiety, which represents the sole point of asymmetry in the system. We therefore undertook variation of the substrate to probe this further. Interestingly, while switching from *N*-PMB to *N*-Bn was found to have relatively little impact (**18a** vs **18b**), moving to *N*-Me led to a large decrease in selectivity in the formation of compound **20** (Scheme 3). Further, moving from *tert*-butyl ester **10b** to the simple methyl ester **10i** again gave a large decrease in regiocontrol in the formation of **21**. Such observations are consistent with a relay of stereochemical information across the molecule via the nitrogen substituent, where both a bulky ester and a relatively large amine moiety are required to in order for the remote source of asymmetry to control which side of the ketone moiety is deprotonated by the incoming base.

With regiocontrolled access to enol triflates **18** established, we next explored their potential for derivatization via Pd-catalysed cross-coupling. This proved successful, with both *N*-benzyl and *N*-PMB systems undergoing Suzuki cross-coupling with a range of aryl and heteroaryl coupling partners as shown by the formation of **19**. Such Pd-catalysed processes offer reliable C-C bond formation for the introduction of additional complexity, and combined with the aforementioned functionalisation and the excellent selectivity obtained in the enol triflate formation, this underlines the versatility of such systems to function as tricyclic 3D scaffolds.

Scheme 4. Direct conversion to [8,5,5]-fused system 23



a) TFA, CH_2Cl_2, 0 °C to rt *then* oxalyl chloride, CH_2Cl_2, 0 °C to rt; b) DBU, MeCN, 80 °C; c) AllylMgBr, THF, 0 °C to rt; d) Pd/C (10%), HCO_2NH_4, MeOH, 60 °C; e) NaHMDS, THF, -78 °C, *then* $PhNTf_2$, to rt; f) $ArB(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, LiCl, 1,4-dioxane, 85 °C; g) Pd/C (10%), HCO_2NH_4, MeOH, 60 °C.

Following this, the previously observed cyclisation to form mesylate **17** led us to consider whether such a bond formation might permit an overall rearrangement within these polycyclic scaffolds. To this end we took PMB amine **10b** and performed ester deprotection followed by activation of the resulting carboxylic acid with thionyl chloride. Gratifyingly, this led to C-N

formation with concurrent cleavage of the adjacent C-N bond, giving rise to a mixture of chloride **22** and alkene **23**. While chloride **22** could be isolated in moderate yield, inclusion of a DBU-mediated elimination as the final stage of this one-pot process allowed the isolation of only alkene **23** in excellent yield in a single operation. This product again represents a novel and rigid scaffold, possessing an unusual 8-membered ring within a tricyclic framework.

Facile derivatization of this system is also possible as shown by the series of reactions in Scheme 4. Addition of allymagnesium bromide proceeded in excellent yield, to give a tertiary alcohol **24** as a 6:1 mixture of diastereomers. Somewhat counterintuitively, addition preferentially occurs to the *endo* rather than *exo* face of the molecule; however, this can be rationalised by the relative flexibility of the 8-membered ring and the preference for orientation of the ketone carbonyl *anti* to the carbonyl of the amide. See SI for full details. Reduction also proved possible, with a simple transfer hydrogenation of the alkene to form compound **25** proving especially facile. This is consistent with the alkene having limited conjugation with the adjacent carbonyl, which is apparent from both the alkenic chemical shifts within the ^{1}H NMR spectrum as well as the alkene's low reactivity in standard cycloaddition processes. Importantly, conversion of the ketone moiety to the corresponding enol triflate again proved facile, giving diene **26** in good yield. This was found to undergo efficient Suzuki cross-coupling to form **27**, thus providing another position for diversification, as well as quantitative reduction via transfer hydrogenation to form the parent system **28**.

In conclusion, successive alkene oxidative cleavage and double Mannich reactions enable the stereoselective transformation of simple norborenes into complex tricyclic alkaloid-like species **10**. The approach represents a one-atom ring expansion with simultaneous annulation and permits direct and scalable synthesis of scaffolds which have been shown to undergo three-fold orthogonal reactivity. The compounds also undergo surprisingly regioselective enol triflate formation, with subsequent cross-coupling adding additional scope for subsequent diversification. Further, the scaffold formed is readily converted into scaffold **23**, which possesses an unusual 8,5,5-tricyclic architecture and is capable of undergoing similarly broad diversification. Given the high levels of diastereocontrol and that methods for performing asymmetric Diels-Alder reactions are well established,[35-37] the methodology also offers the potential to access complex, enantioenriched scaffolds. Use of such oxidative cleavage/double Mannich sequences need not be limited to norbornene-derived alkenes, and studies of the scope of this one-atom ring expansion/annulation methodology are underway.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ASSOCIATED CONTENT

Supporting Information

Figures, tables, experimental details and characterization data for all new compounds (PDF)

Accession Codes

CCDC 2346821-2346823 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033

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