Multicomponent Reactions

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A Bioinspired Ugi/Michael/Aza-Michael Cascade Reaction in Aqueous Media: Natural-Product-like Molecular Diversity**

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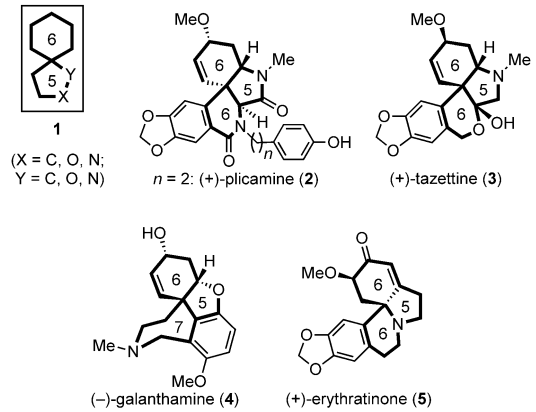
The rapid construction of diverse and complex molecular architectures requires a milieu of chemical knowledge poised for undertaking synthetic challenges.[1–3] As an example, biologically relevant spirocyclic frameworks possessing quaternary carbon centers that assemble in a regio- and stereospecific manner from simple substrates have seen substantial advancements over the years.[4] In this light, multicomponent reactions (MCRs) that concomitantly involve cascade processes have emerged as powerful strategies for assembling higher-ordered structures.[5] These reactions can sequentially generate multiple stereocenters in a single transformation,[6] thus bypassing time-consuming and costly purification.[7] Ultimately, strategizing cascade processes from MCRs, in which the theme of constructing complex molecular architectures is engaged, provides a substantial challenge in modern-day organic chemistry.

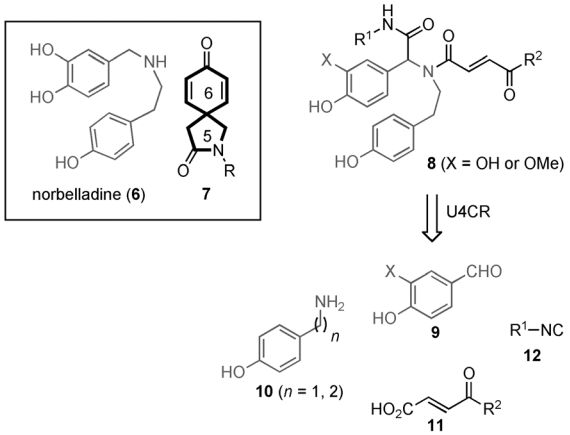
As a part of an ongoing research program toward the development of unique cascade reactions using MCRs to generate biologically relevant, diverse, small, and complex molecules, we were particularly interested in spirocyclic-architecture-containing aza- and/or oxaspiro[4.5]decanes (**1**; Scheme 1).[8] Thus, we embarked on devising a synthetic strategy for the construction of *Amaryllidaceae* alkaloids (+)-plicamine (**2**),[9] (+)-tazettine (**3**),[10] (−)-galanthamine (**4**; Reminyl, Razadyne, Nivalin),[11] and *Erythrina* alkaloid (+)-erythratinone (**5**;[12] Scheme 1), as these and other family members exhibit anticholinergic, antitumor, anticancer, immunosuppressive, and analgesic properties.[13] In addition, members of this family are known to inhibit various cell-cycle progressions (e.g., G_o/G_1 phase in tumor progression, G_2/M phase in HIV-1), and have found applications in the therapeutic treatment of schizophrenia and Alzheimer's disease.[13]

Compounds **2**–**5** all possess tetracyclic nitrogenous structures containing a 5,6,6- or 5,7,6-fused azaspiro cyclic core that underpins a quaternary carbon center, with **5** as the lone exception. In 1957, Barton proposed that all the *Amaryllidaceae* alkaloids were derived from the common bisphenol biosynthetic precursor norbelladine (**6**),[14] which is assembled from amino acids L-Phe and L-Tyr (Scheme 2). Most recently, this hypothesis was validated by Oppolzer and co-workers.[15] One of the major challenges for their synthesis was the construction of a highly congested quaternary center such as in **1**. This key framework has been typically synthesized by using hypervalent iodine (e.g., phenyliodine(III) bis(trifluoroacetate) (PIFA), (diacetoxyiodo)benzene (DIB)), ICl, or metal reagents.[16]



Scheme 1. Bioactive fused azaspiro polycyclic alkaloids (**2**–**5**).

Recently, we reported that a 2-azaspiro[4.5]deca-6,9-diene-3,8-dione framework (**7**; Scheme 2) could be constructed by a single synthetic transformation using bifunctional substrates in the absence of any additive reagents with water as the solvent.[17] Inspired by the amino acid biosynthetic pathway as well as by the work of Ley and co-workers,[9] we envisioned that an Ugi four-component reaction (U4CR)



Scheme 2. Similarity between norbelladine (**6**) and compound **8**.

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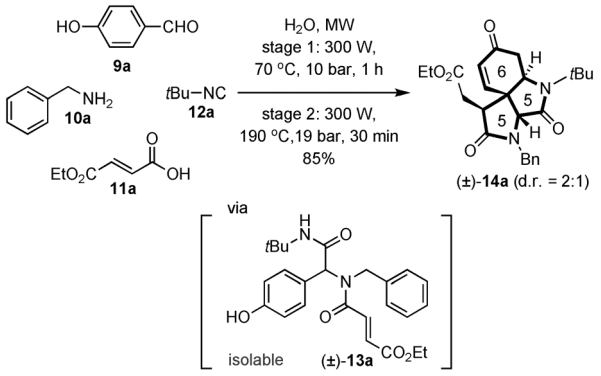
could generate an acyclic product such as dipeptide **8** (Scheme 2), which would be similar to **6** and poised to undergo phenolic oxidative coupling, thus mimiking the proposed alkaloid biogenesis process.

In order to test our hypothesis, we initially selected *p*-hydroxybenzaldehyde (**9a**), benzylamine (**10a**), fumaric acid monoethyl ester (**11a**), and *tert*-butyl isocyanide (**12a**) as the coupling reagents, and subjected the mixture to microwave (MW) irradiation[18] in methanol at 300 W, 200 °C, 18 bar for 20 min. The reaction gave rise to 5,5,6-fused azaspiro tricycle **14a** in approximately 10% yield (Scheme 3), along with undesired side products. As we initially expected to observe a 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (such as **7**), we were



Scheme 3. Formation of 5,5,6-fused azaspiro tricycle **14a**.

enlightened to fully characterize **14a**. Recognizing that water would accelerate the overall process,[19] we screened the reaction in methanol/water (10–100% water) by using various temperature, pressure, and time[20] combinations. An improved yield of **14a** (ca. 70%) was obtained when the microwave was equilibrated to 300 W, 190 °C, 19 bar for 30 min. However, in order to avoid any unwanted Passerini side product[21] or *N*-formylamide formation,[22] we elected to carry out the reaction in water alone by utilizing a two-stage protocol (stage 1: 70 °C, 10 bar, 1 h; stage 2: 300 W, 190 °C, 19 bar, 30 min), which further improved the yield to 85% and avoided the formation of unwanted by-products.

In an attempt to pinpoint atom connectivity in the cascade process and deduce mechanistic insights, the reaction was first repeated with preformed acyclic Ugi product **13a**,[20] which ultimately provided **14a** in similar yield. The result implied that an initial Ugi reaction had occurred as the first reaction in the Ugi/Michael/aza-Michael (UMAM) sequence of reaction transformations.[17]

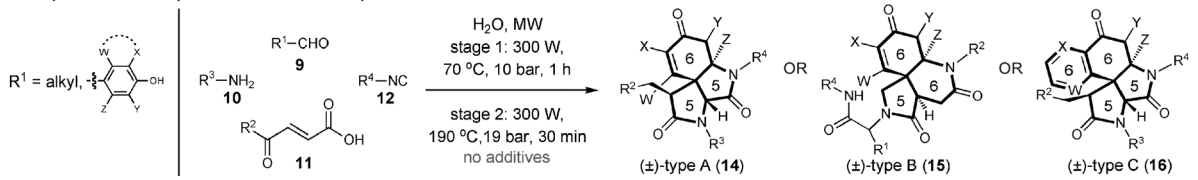
We next examined the scope of the reaction by using various substrates. As noted in Table 1, we observed that electron-donating substituents on the trifunctional *p*-hydroxybenzaldehyde (e.g., OMe; Table 1, entries 1, 2, 4–6, 8–10) favor the formation of fused azaspiro tricycles (**14**, type A), while electron withdrawing NO_2 and Br substituents lead to severe decomposition.

In contrast, 3-fluoro-*p*-hydroxybenzaldehyde (**9f**) provided the desired fused azaspiro tricycle **14h** in appreciable yield (Table 1, entry 7). Use of very bulky substituents on the isocyanide group, such as adamantyl (**12c**; Table 1, entry 4), resulted in the single isomer **14e**. Replacement of fumaric acid monoethyl ester (**11a**) with trifunctional *N*-methylmaleamic acid (**11d**; Table 1, entry 11) resulted in the corresponding 5,6,6-fused azaspiro tricycle **15a** (type B) in good yield. Remarkably, use of 4-hydroxy-1-napthaldehyde (**9h**) resulted in 5,5,6,6-fused azaspiro tetracycles **16a** and **16b** (type C) in greater than 98:1 diastereoselectivity (Table 1, entry 12 (product confirmed by X-ray crystal structure) and entry 13). Importantly, the reaction did not occur when other heating sources were used, although our attempts were limited in scope. Remarkably, however, the reaction afforded a quantitative yield of spirocycle **18** when run under stage 1 conditions. This result could be attributed to the fact that the 5-*exo-trig* Michael addition retains complete aromaticity of an intact benzene ring.[20] In all successful instances, the complexity of the products that result from this cascade UMAM reaction illustrates the remarkable chemo-, regio-, and stereoselectivity achieved by using simple and readily available materials without protecting-group manipulation.

We rationalized that the acyclic Ugi product could exist either in *trans*-amide (**13′**) or *cis*-amide (**13″**) conformations at room temperature. In the *trans*-amide conformation, an electron-donating *p*-hydroxy group on **9** (R^1) would lead to the formation of 2-azaspiro[4.5]deca-6,9-diene-3,8-dione (**18**) through a 5-*exo-trig* Michael addition of **17** (Scheme 4) under the influence of microwave irradiation. We noted that the formation of **18** was controlled by the substituents at R^4.[17] Bulky groups favor the formation of **18** because of steric effects, and disfavor the formation of DKP **21** as the competing pathway. Since bulky R^4 substituents hinder the progression of a 6-*exo-trig* aza-Michael addition, we propose that the unprecedented 5-*exo-trig* aza-Michael addition on intermediate **18** occurs as a result of the proximity effect,[23] and ultimately gives rise to (±)-type A and (±)-type C products. Both zwitterionic intermediates **17** and **19** are believed to be stabilized by hydrogen bonding and help to absorb microwave energy efficiently.[24] To the best of our knowledge, this is a rare example in which the same substituent directs a specific reaction outcome and then simultaneously participates in a bond-forming reaction solely because of steric effects. On the other hand, the less bulky group at R^2 (Table 1, entry 11) led to the formation of (±)-type B through a 6-*exo-trig* aza-Michael pathway.[25] Importantly, when X = OMe, the 5-*exo-trig* aza-Michael addition occurred regioselectively on the carbon atom bearing Z of the more reactive Michael acceptor. Structural characterization and relative stereochemistry of the fused azaspiro tricycles and azaspiro tetracycles were established by NOE, ^1H–^1H gDQFCOSY, gHMQC, and gHMBC experiments, and unequivocally confirmed by X-ray crystal structure analysis.[20]

Although Baldwin's rules favor both 6-*exo-trig* and 7-*exo-trig* ring cyclization events,[23] it is noteworthy that 2,5-DKPs (**21**), 5,6,7-fused azaspiro tricycle **23**, or a 5,6,6,7-fused azaspiro tetracycle **24** were not obtained when R^4 was a bulky *tert*-butyl group (Schemes 4 and 5). However, a 6-*exo-trig* aza-Michael pathway was favored when substrates **9g**, **10c**, **11d**, and **12a** were used (Table 1, entry 11).[25] Our

Table 1: Scope of the one-pot UMAM cascade process.



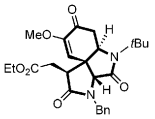
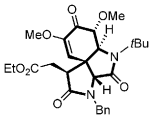
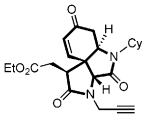
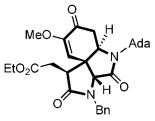
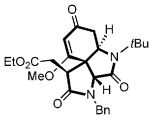
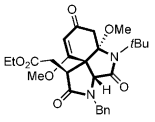
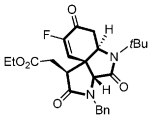
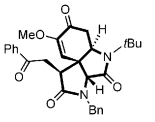
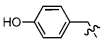
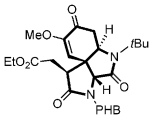
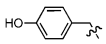
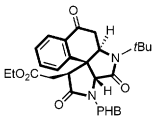
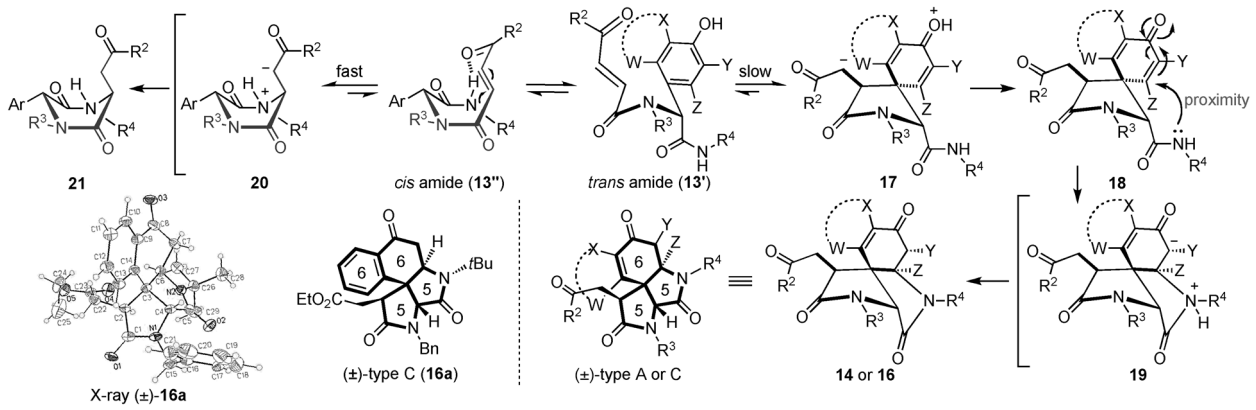
Entry	R^1		R^2		R^3		R^4		Product		Type/Yield[a] [%]/d.r.[b]
1		**9b**	OEt	**11a**		**10a**		**12a**		**14b**	A/85/3:1
2		**9c**	OEt	**11a**		**10a**		**12a**		**14c**	A/89/3:1
3[c]		**9a**	OEt	**11a**		**10b**		**12b**		**14d**	A/90/3:1
4		**9b**	OEt	**11a**		**10a**		**12c**		**14e**	A/65/single diastereomer
5		**9d**	OEt	**11a**		**10a**		**12a**		**14f**	A/85/10:1
6		**9e**	OEt	**11a**		**10a**		**12a**		**14g**	A/80/9:1
7		**9f**	OEt	**11a**		**10a**		**12a**		**14h**	A/70/3:1
8		**9b**	Ph	**11b**		**10a**		**12a**		**14i**	A/84/6:1
9		**9b**	OEt	**11a**		**10c**		**12a**		**14j**	A/81/3:1
10		**9b**	*p*-MeC_6H_4	**11c**		**10d**		**12a**		**14k**	A/82/5:1
11		**9g**	NHMe	**11d**		**10c**		**12a**		**15a**	B/82/2:1
12[d]		**9h**	OEt	**11a**		**10a**		**12a**		**16a**	C/99/99:1[e]

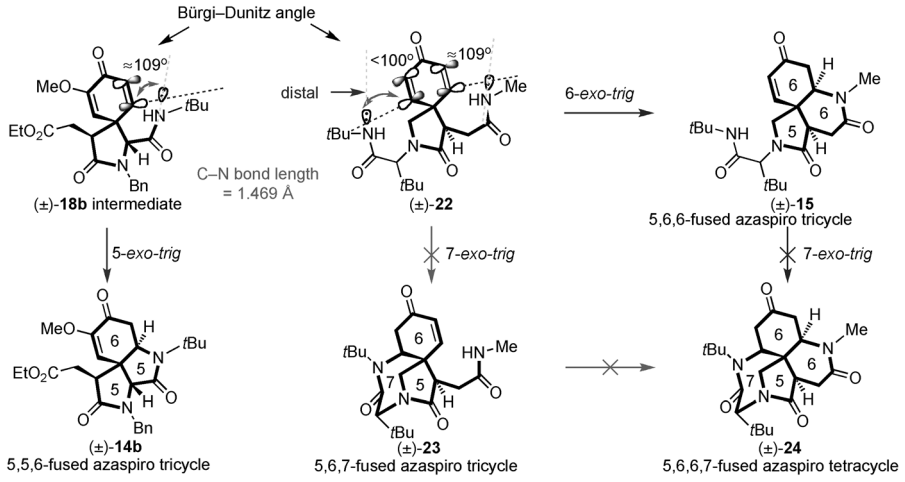
Table 1: (Continued)

Entry	R^1	R^2	R^3	R^4	Product	Type/Yield[a] [%]/d.r.[b]
13[d]	 **9h**	OEt	**11a** 	**10c** 	**12a** 	**16b** C/99/98:1

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy ($T_1 = 2.5$ sec). [c] Approximately 3% diketopiperazine (DKP) **21** (see Scheme 4) was isolated. [d] Isolable compound **18** was formed in stage 1 (see Scheme 4). [e] Structure confirmed by X-ray crystallography.



Scheme 4. Proposed mechanism for the cascade UMAM reaction.



Scheme 5. Bürgi–Dunitz trajectory and proximity effect.[23a]

rationale is illustrated in Scheme 5 and argues that the Bürgi–Dunitz angle takes precedence in the cyclization event that leads to the more favorable type A or B or C convention. When R^4 is *tert*-butyl, an unfavorable spatial orientation of the nucleophile (lone pair of electrons on the nitrogen atom, highest occupied molecular orbital, HOMO) and the electrophile (C=C π^* orbital of the Michael acceptor, lowest unoccupied molecular orbital, LUMO) does not allow for the 7-*exo-trig* aza-Michael pathway (**22**→**23**) either because of steric effects or lack of effective orbital overlap. On the other hand, the Bürgi–Dunitz angle of attack is favorable for a 5-*exo-trig* (**18b**→**14b**, when R^4 is a bulky group) or 6-*exo-trig* cyclization (**22**→**15**, when R^2 is a less bulky group) because of an effective overlap between the HOMO and the LUMO.[23]

In conclusion, we have developed a unique Ugi/Michael/aza-Michael (UMAM) cascade reaction for the synthesis of natural-product-like[26] fused azaspiro tricycles and azaspiro tetracycles by using microwave irradiation, in the absence of any additives, with water as the solvent. Remarkably, this cascade process generates a quaternary center, four stereogenic centers, and six contiguous bonds, and provides good to excellent yields as well as regioselectivities with appreciable diastereoselectivity. Further functional and structural diversity can be achieved from these compounds by chemical manipulation as well as by employing suitable convertible isocyanides. The continuing work on this highly unusual chemistry will focus on: 1) the total synthesis of plicamine, 2) biological evaluation including structure–activity-relationship (SAR) studies, and 3) stereochemical control of the U4CR.

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