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A Stereodivergent Strategy for the Preparation of Corynantheine and Ipecac Alkaloids, Their Epimers, and Analogues: Efficient Total Synthesis of (−)-Dihydrocorynantheol, (−)-Corynantheol, (−)-Protoemetinol, (−)-Corynantheal, (−)-Protoemetine, and Related Natural and Nonnatural Compounds

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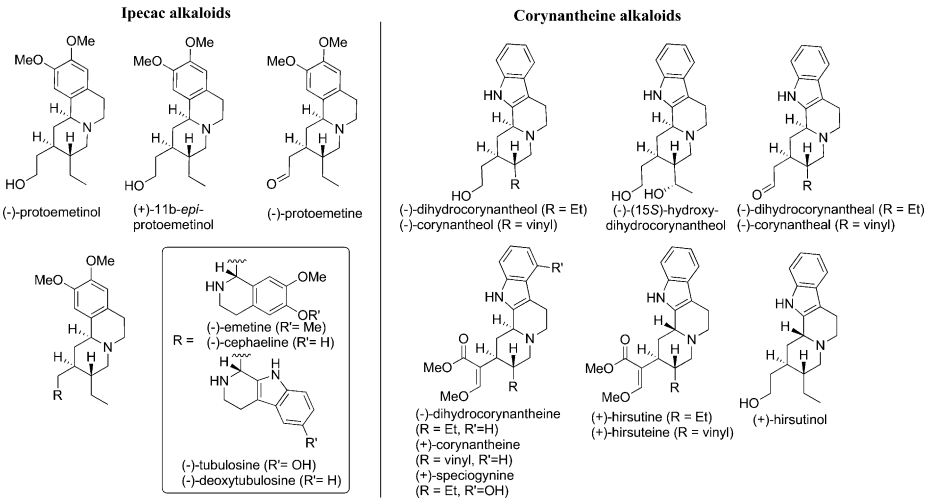
Abstract: Here we present a general and common catalytic asymmetric strategy for the total and formal synthesis of a broad number of optically active natural products from the corynantheine and ipecac alkaloid families, for example, indolo[2,3-*a*]- and benzo[*a*]quinolizidines. Construction of the core alkaloid skeletons with the correct absolute and relative stereochemistry relies on an enantioselective and diastereodivergent one-pot cascade sequence followed by an additional diastereodivergent reaction step. This allows for enantio- and diastereoselective synthesis of three out of four possible epimers of the quinolizidine alkaloids that begin from common and easily accessible starting materials by using a common synthetic route. Focus has been made on excluding protecting groups and limiting isolation and purification of synthetic intermediates. This methodology is applied in the total synthesis of the natural products (−)-dihydrocorynantheol, (−)-hirsutinol, (−)-corynantheol, (−)-protoemetinol, (−)-dihydrocorynantheal, (−)-corynantheal, (−)-protoemetine, (−)-(15*S*)-hydroxydihydrocorynantheol, and an array of their nonnatural epimers. The potential of this strategy is also demonstrated in the synthesis of biologically interesting natural product analogues not accessible through synthetic elaboration of alkaloid precursors available from nature, for example, thieno[3,2-*a*]quinolizidine derivatives. We also report the formal synthesis of (+)-dihydrocorynantheine, (−)-emetine, (−)-cephaeline, (−)-tubulosine, and (−)-deoxytubulosine.

Keywords: alkaloids · asymmetric catalysis · diastereodivergency · natural products · total synthesis

Introduction

The corynantheine and ipecac alkaloid families contain a vast number of naturally occurring compounds that share a quinolizidine structural motif. They are mainly isolated from the leaves of *Uncaria tomentosa* (cat claw) and the root of *Cephaelis ipecacuanha* (Rubiaceae) and have a long history of usage as herbal drugs to treat inflammation, rheumatism, gastric ulcers, tumors, dysentery, as birth control, and to promote wound healing. Over the years there have been several studies on the pharmacological properties of the individual alkaloids, which have been shown to possess considerably diverse and interesting biological activity. For example, high antiviral activity is observed for the indoloquinolizidines of the corynantheine group, dihydrocorynantheine and hirsutine, towards influenza virus type A.[1] The corynantheine family also exhibits anti-inflammatory,[2] antiarthritic,[3] antibacterial,[4] analge-



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sic,[5] and antiallergenic[6] activity. Tubulosine, emetine, and cephaeline, from the ipecac alkaloid families, are potent inhibitors of protein biosynthesis.[7] Remarkable activities against several cancer-cell lines,[8] for example, lymphatic leukemia,[9] HIV reverse-transcriptase inhibitory activities,[10] antiprotozoic properties,[11] as well as antiamoebic activity have also been observed. Emetine also has a history as a therapeutic emetic. In nature, both corynantheine and ipecac alkaloids share the same biosynthetic pathway and are formed through the enzymatic condensation of the monoterpene secologanin with tryptamine and dopamine, respectively.[12,13] From a synthetic point of view, construction of the fused-ring system with control of the relative and absolute stereochemistry on the quinolizidine core structure represents a significant challenge and considerable research focus has been placed on its laboratory preparation. Traditionally, the majority of previously reported strategies for the asymmetric total synthesis of quinolizidine alkaloids have required a multistep synthesis that relies on starting materials from the chiral pool.[14] These strategies often include several functional group transformations and tedious protection/deprotection steps. As a consequence, the enantioselective total syntheses of corynantheine and ipecac alkaloids and analogues thereof are demanding and proceed in low overall yield. Lately, there have been a few scattered reports of efficient synthesis of optically active quinolizidine natural products and different analogues based on asymmetric catalysis.[15–18] Worthy of mention is the elegant total synthesis of *ent*-dihydrocorynantheol by Itoh et al.[17f] The key step in their strategy is based on an enantioselective proline-catalyzed annulation of 3-ethyl-3-buten-2-one to 9-tosyl-3,4-dihydro-β-carboline, which provides the target alkaloid in only three additional steps. Although highly efficient and productive, the majority of the synthetic strategies developed is target-specific with respect to the relative configuration of the quinolizidine stereocenters and only allow for selective formation of one specific epimer of the alkaloid.[19]

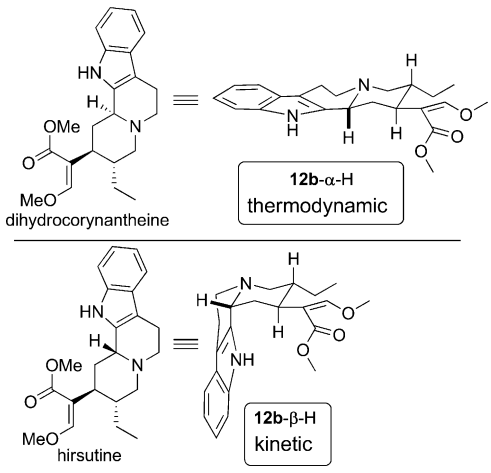
Keeping in mind the structural similarity of the quinolizidine alkaloids, we anticipated that an array of naturally occurring quinolizidine alkaloids, their epimers, and analogues, including those not accessible through the synthetic elaboration of naturally occurring alkaloids, could be prepared by means of a single and general synthetic strategy. Our plan was to develop a common synthetic route to a series of functionalized quinolizidine intermediates with skeletal and stereochemical variation. These epimerically different intermediates are to be designed in such a way that they can be rapidly modified in a few synthetic operations to the desired alkaloids with correct absolute and relative stereochemistry. We were also determined to put considerable focus on the overall efficiency of the synthetic strategy through the implementation of asymmetric one-pot and cascade/tandem reactions.[20,21] Such strategies will have the advantage of avoiding traditional stop-and-go synthesis,[22] which will reduce the tedious isolation and purification of synthetic intermediates and result in higher-yielding processes that will allow for practical quantitative preparation of the alkaloids.

To meet the requirements for efficient and diverse quantitative total synthesis, we set the following objectives: 1) readily available starting materials, not limited by the chiral pool; 2) easily manageable operational protocols on a multigram scale; 3) selective access to different diastereoisomers through stereodivergent reaction steps; 4) low number of synthetic operations, isolationism and purifications of reaction intermediates; 5) no protection/deprotection of functional groups; and 6) easy access to nonnatural quinolizidine alkaloid analogues.

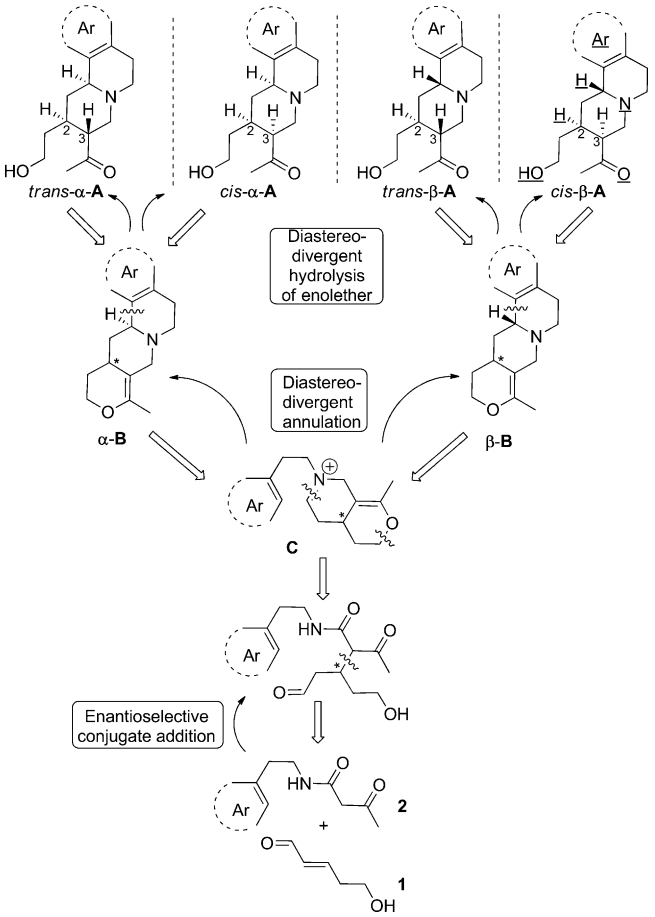
Here we wish to report an enantioselective and diastereodivergent synthetic strategy for quantitative preparation of a broad variety of alkaloids that contain a quinolizidine substructure that we believe fulfills the above-mentioned criteria.

Results and Discussion

Retrosynthetic analysis: The common structural unit for the corynantheine and ipecac alkaloids is the quinolizidine ring, which contains a fused aromatic group and three stereocenters wherein one is a ring-junction stereocenter. The ring-junction stereocenter has a great impact on the conformation of the alkaloid as can be seen through comparison of the two naturally occurring ring-junction epimers, dihydrocorynantheine and hirsutine, in which the former is the thermodynamically most stable form and has all groups on the quinolizidine substructure in the equatorial position (Scheme 1).[23] Hirsutine, on the other hand, has the aromatic group in an axial position that forces a V-shaped form. Interestingly, dihydrocorynantheine and hirsutine have been found to have differing biological activities,[24] thus stereoselective formation of different epimers is highly desired. This requires special considerations during synthesis and has been one of the bottlenecks in previously reported total syntheses of quinolizidine alkaloids.[14i] We came to the conclu-

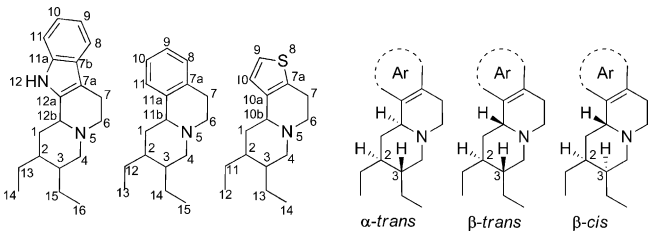


Scheme 1. Conformations of the epimeric natural products **12b**-α-H dihydrocorynantheine and **12b**-β-H hirsutine.



Scheme 2. Stereodivergent retrosynthetic analysis of quinolizidine alkaloids.

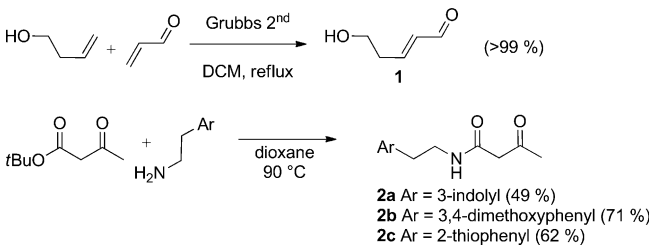
sion that the four different epimers of quinolizidine derivatives **A** would be prominent precursors for a broad series of corynantheine and ipecac alkaloids, their epimers, and different analogues (Schemes 2 and 3). The strategy should be based on asymmetric catalysis, and we also envisioned a



Scheme 3. Nomenclature used through this paper (α and β refers to the ring-junction configuration, *trans* and *cis* refers to the relative relationship between C^2 and C^3).

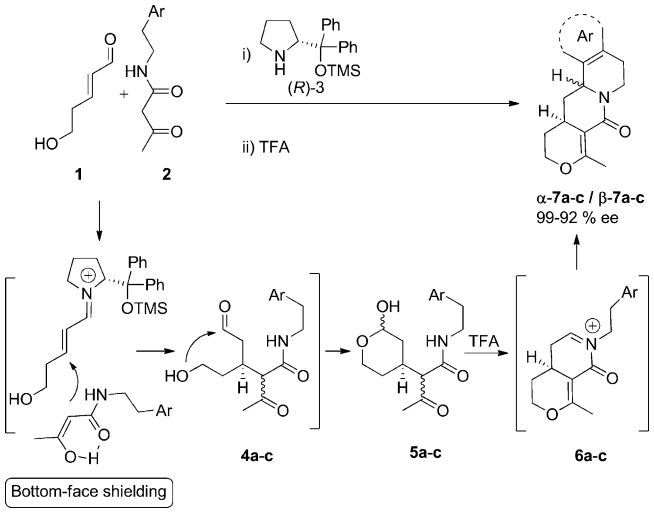
stereodivergent introduction of the following stereocenters by taking advantage of thermodynamic and kinetic reaction conditions. This will allow for fast construction of different epimeric intermediates from common starting materials. We anticipated that it would be possible to hydrolyze the enol ether moiety of compound **B** in a diastereodivergent matter, thus achieving the C^2–C^3 *cis* or *trans* configuration. From compound **B**, our first C–C bond disconnection leads back to the *N*-acyliminium ion **C**. On the basis of our previous developments in stereoselective *N*-acyliminium ion cyclizations, we proposed that the annulation could be controlled to give either the α- or β-epimer in a second diastereodivergent reaction.[25,26,27b] Further disconnections led back to the α,β-unsaturated aldehyde **1** and β-ketoamide **2**. We reasoned that optical activity could be introduced in the first step through an enantioselective organocatalytic conjugate addition (Scheme 2).[28] The catalytic asymmetric conjugate addition of amidomalonates to α,β-unsaturated aldehydes has been previously studied by Rios et al.[29] and our group.[27] However, this reaction is limited to cinnamic aldehyde derivatives, and attempts to use alkyl-substituted α,β-unsaturated aldehydes resulted in decomposition of the aldehyde. This drastically limits the potential use of this reaction in quinolizidine natural-product synthesis. We reasoned that the reluctance of amidomalonates to undergo conjugate addition to alkyl-substituted α,β-unsaturated aldehydes was mainly due to the poorer stability of alkyl-substituted α,β-unsaturated aldehydes relative to cinnamic aldehydes and the low nucleophilicity of the amidomalonate. To circumvent this, we attempted to use the more nucleophilic β-ketoamide in the conjugate addition.

One-pot stereoselective construction of the quinolizidine carbon skeleton: Our retrosynthetic analysis leads back to the α,β-unsaturated aldehyde **1**, which was easily accessible through the cross-metathesis of acroleine and 3-butenol by using only 0.7 mol% Grubbs second-generation catalyst in almost quantitative yield. The β-ketoamides **2a–c** were accessed through the condensation of *tert*-butyl acetoacetate with the corresponding 2-arylethanamine (Scheme 4).



Scheme 4. Starting material synthesis. DCM = dichloromethane.

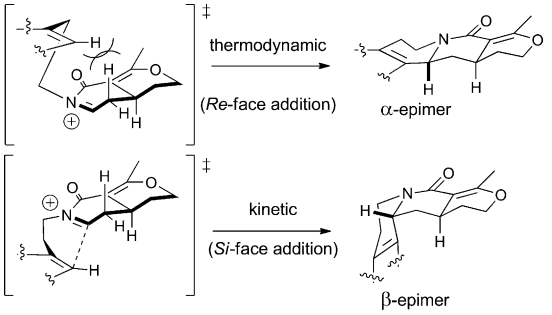
Gratifyingly, we found that β-ketoamides **2a–c** smoothly reacted with the α,β-unsaturated aldehyde **1** in the presence of catalyst **3** to give a white precipitate that indicated that the conjugate addition had gone to completion. An analytical sample of the formed precipitate was analyzed by ^{1}H NMR spectroscopy, which established it as a diastereomeric mixture of lactols **5a–c** (Scheme 5). The crude reaction mixture that contained the lactol **5a–c** was quenched by addition of trifluoroacetic acid (TFA) to give a 1:1 mixture of the two ring-junction isomers α-**7a–c** and β-**7a–c**, which could be isolated in good yields and high enantioselectivity



Scheme 5. Proposed mechanism for one-pot quinolizidine synthesis.

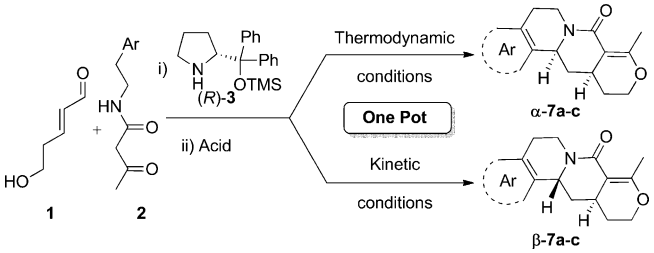
in a two-step one-pot process (Scheme 5 and Table 1).[30] The mechanism for this reaction is proposed to proceed through iminium ion activation and conjugate addition to give **4**. The sterically shielding groups on the catalyst will shield the *Re* face of the intermediate iminium ion, thus favoring the nucleophilic attack of the β-ketoamides from the *Si* face and generating the C^1 stereocenter with the desired absolute configuration.[31] Spontaneous cyclization gives the intermediate lactol **5** (Scheme 5). The addition of TFA to lactol **5** triggers an acid-catalyzed cascade reaction that consists of lactol ring opening, enol ether formation, hemiaminal formation, and acid-catalyzed elimination of water to give *N*-acyliminium ion **6**. Subsequent *N*-acyliminium ion cyclization gives a mixture of α-**7a–c** and β-**7a–c**.[32]

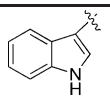
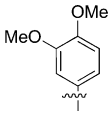
The ring-junction stereocenter is formed through the *N*-acyliminium ion cyclization: reactions that are known to be under kinetic control.[33] Through examination of the expected transition states in the *N*-acyliminium ion cyclization, we reasoned that the kinetically favored ring-junction configuration should be formed through *Si* face addition to lead to formation of the β-epimer (Scheme 6). Confident that the



Scheme 6. Proposed transition states in the formation of thermodynamically and kinetically favored ring-junction epimers in *N*-acyliminium ion cyclization.

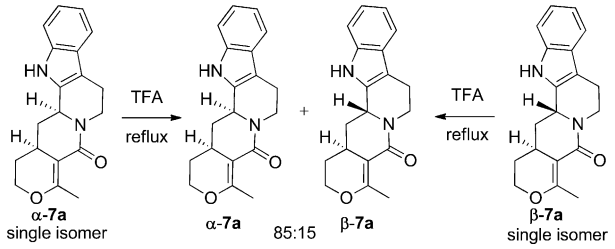
Table 1. Enantio and diastereoselective one-pot formation of both ring-junction epimers of the indolo[2,3-*a*]-, benzo[*a*]-, and thieno[3,2-*a*]quinolizidine skeleton.[a]



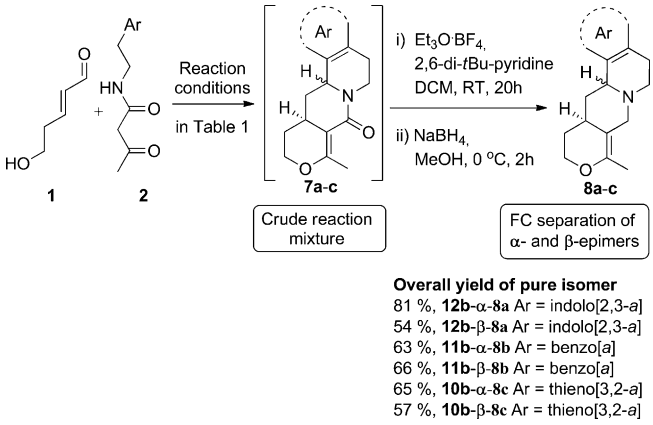
	Ar	Product	Acid	d.r.[b]	*ee* [%][c]	Yield [%][d]
1			TFA	50:50	92	80
2		α-**7a**	AcCl	>95:5	92 (99)[f]	85
3		ß-**7a**	BzCl[e]	18:82	92 (95)[f]	70
4		α-**7b**	$Et_3O{\cdot}BF_4$	70:30	92	73
5		ß-**7b**	$SnCl_4$	22:78	92	76
6		α-**7c**	$Et_3O{\cdot}BF_4$	67:33	95	94
7		ß-**7c**	BzCl	33:67	94	78

[a] A solution of aldehyde **1** (1.2 equiv), amide **2** (1 equiv), and catalyst **3** (20 mol%) in CH_2Cl_2 (1 M) was stirred at room temperature. After full conversion of **2**, the given acid was added to the reaction mixture. [b] Determined by ^1H NMR spectroscopy on the crude reaction mixture. [c] Determined by chiral HPLC on the major diastereoisomer. [d] Isolated combined yields of both epimers. [e] Benzoyl chloride was added at −78°C and stirred for 4 h before being slowly allowed to reach room temperature over 4 h. [f] A solution of aldehyde **1** (1.2 equiv), amide **2a** (1 equiv), and catalyst **3** (20 mol%) in CH_2Cl_2 (1 M) was stirred at −20°C for 72 h.

diastereoselectivity in this step could be controlled to favor selective formation of the α- or the β-ring-junction epimer through kinetic or thermodynamic control, we set out to find a series of acid conditions for the one-pot cascade. This turned out to be a considerably challenging task and no real trends could be observed, with most acids giving a close to 1:1 diastereomeric ratio.[34] After extensive screening, we found a series of conditions that allowed for a diastereomeric switch (Table 1). Thus, quenching the reaction of β-ketoamide **2a** with acetyl chloride resulted in the formation of a precipitate that was found to be the thermodynamically favored indolo[2,3-*a*]quinolizidine α-**7a** as the only observable isomer (Table 1, entry 2). Interestingly, when using benzoyl chloride, we observed a switch in diastereoselectivity and the kinetically favored product β-**7a** was obtained as the major isomer in 82:18 diastereoselectivity (entry 3). It is also worth noting that the kinetically favored β-indolo[2,3-*a*]quinolizidine β-**7a** could be epimerized to the thermodynamically favored α-**7a** epimer by treatment with TFA heated at reflux to give a ratio of 85:15 in favor of the α-epimer (Scheme 7). When subjecting the pure thermodynamically favored α-**7a** epimer to TFA heated at reflux, the same thermodynamic equilibrium was reached. Since a higher preference for the α-**7a** epimer was obtained by using acetyl chloride than under thermodynamic equilibrium



Scheme 7. Acid-catalyzed epimerization of α- and β-indolo[2,3-*a*]quinolizidine **7a**.

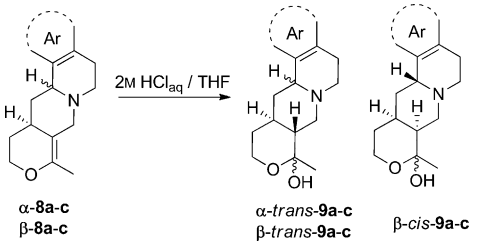


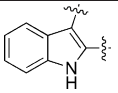
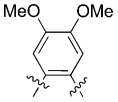
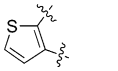
Scheme 8. Enantio- and diastereoselective synthesis of the quinolizidine skeleton.

conditions (see Table 1, entry 2 and Scheme 7), it appears as the acetyl chloride-promoted *N*-acyliminium ion cyclization is not under thermodynamic control, which leads us to believe that the high selectivity observed is due to the precipitation of the thermodynamically favored α-**7a** epimer during the reaction. Unfortunately, the optimized acid conditions for the indole compound could not be directly applied to selective ring-junction formation of the benzo[*a*]- or the thieno[3,2-*a*]quinolizidines **7b**,**c**, so a new acid screening was conducted. As for the initial screening of the indole compound, the one-pot cascade using the phenyl- and thiophenyl-ketoamides **2b**,**c** gave poor selectivity in the formation of the ring-junction stereocenter by using a variety of different acid conditions. Eventually, we found that triethyloxonium tetrafluoroborate promoted the formation of the thermodynamically favored ring-junction stereocenter α-**7b**,**c** with moderate selectivity (entries 4–6). One-pot conditions that favored the kinetic epimers benzo[*a*]- and thieno[3,2-*a*]quinolizidines β-**7b**,**c** with moderate selectivity were identified to be tin(IV) chloride and benzoyl chloride, respectively (entries 5–7). The exact role of the acid with respect to selectivity in the formation of the ring-junction stereocenter is not clear, and we have not been able to detect any obvious trends between different acids during screening.[34]

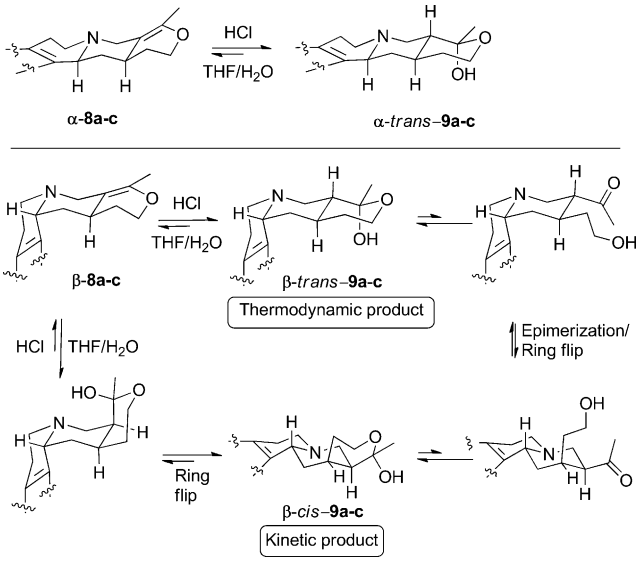
Preparation of functionalized quinolizidine intermediates: After establishing an efficient and stereoselective method for the preparation of alkaloid carbon skeletons **7a–c**, we started to investigate how these intermediates could be applied in total synthesis. To obtain the desired natural products, we needed to reduce both the amide carbonyl and the masked carbonyl group in the dihydropyran moiety. Our main focus from this point on was to develop an efficient methodology that used as few reaction steps as possible, and to limit the number of isolations and purifications of reaction intermediates. We also needed to consider separation of the undesired ring-junction diastereoisomers as early as possible in the reaction sequence. It appeared that the α- and β-epimers of amides **7a–c** could not be easily separated on flash column; however, reduction of the crude reaction mixture from the one-pot cascade was accomplished by initial alkylation with triethyloxonium tetrafluoroborate, followed by $NaBH_4$ reduction to give the corresponding amines **8a–c** in high to moderate overall yields from their corresponding β-ketoamide **2** (Scheme 8). At this stage, the α- and β-epimers of amines **8a**,**b** could be easily separated by flash column. Next we needed to open the dihydropyran moiety, bearing in mind selective formation of the final stereocenter. Treatment of the α-epimers of amines α-**8a–c** with HCl in water/THF at room temperature gave the *trans* ring junction of the lactol α-*trans*-**9a–c** exclusively (Table 2, entries 1, 4, and 7; for nomenclature, see Scheme 3). The selective formation of this stereocenter is due to the thermodynamic stability of the all-equatorial quinolizidine structure, and attempts to access the α-*cis* configuration have failed (Scheme 9). However, hydration of the dihydropyran in the kinetic β-epimer series turned out to be under kinetic and

Table 2. Diastereodivergent lactol formation.[a]



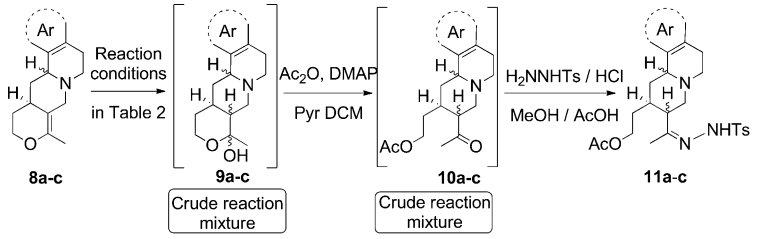
	Ar	Starting material	*T* [°C]	ratio[b] *trans*/*cis*	Product
1		α-**8a**	RT	>95:5	α-*trans*-**9a**
2		β-**8a**	65	83:17	β-*trans*-**9a**
3		β-**8a**	0	20:80	β-*cis*-**9a**
4		α-**8b**	RT	>95:5	α-*trans*-**9b**
5		β-**8b**	65	71:29	β-*trans*-**9b**
6		β-**8b**	0	<5:95	β-*cis*-**9b**
7		α-**8c**	RT	>95:5	α-*trans*-**9c**
8		β-**8c**	65	72:28	β-*trans*-**9c**
9		β-**8c**	0	<5:95	β-*cis*-**9c**

[a] Compound **6** was dissolved in 2 M $HCl_{(aq)}$/THF (1:3 $c = 0.1$ M) at the given temperature. [b] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture.



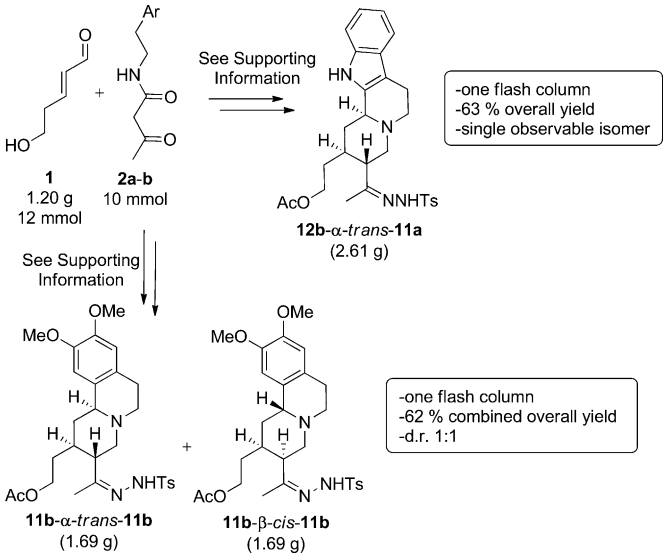
Scheme 9. Stereoselective hydration of enol ether.

thermodynamic control, and treatment of benzo[*a*]quinolizidine and thieno[3,2-*a*]quinolizidine β-**9b**,**c** with HCl in water/THF at room temperature favored the *cis* configuration between C^2–C^3 and gave a 2:1 mixture of β-*cis*-**9b**,**c** and β-*trans*-**9b**,**c**. Further optimization of the hydration revealed that treatment of β-**8b**,**c** with HCl in water/THF at 0 °C exclusively gave the C^2–C^3 *cis* configuration and β-*cis*-**9b**,**c** were obtained as the only observed isomers (entries 6 and 9). The indolo[2,3-*a*]quinolizidine β-**8a** reacted with lower selectivity in this reaction and gave a 4:1 mixture of β-*cis*-**9a** and β-*trans*-**9a** (entry 3). Interestingly, lactol formation at elevated temperatures (HCl in water/THF at 65 °C) reversed the selectivity and favored formation of benzo[*a*]quinolizidine and thieno[3,2-*a*]quinolizidine β-*trans*-**9b**-**c** in a 5:2 ratio (entries 5 and 8). The indolo[2,3-*a*]quinolizidine β-**8a** showed higher selectivity under these reaction conditions, and β-*trans*-**9a** was favored with a corresponding 5:1 diastereomeric ratio (d.r.; entry 2). Furthermore, we found that the pure β-*cis*-**9a**–**c** epimers could be smoothly epimerized in HCl_{aq}/THF at 65 °C to give β-*trans*-**9a**–**c** in the same diastereomeric ratio as was observed for the acid catalyzed hydration of β-**9a**–**c**, thereby indicating that β-*trans*-**9a**–**c** is the thermodynamically favored isomer. Our assumption is that the epimerization is driven through the open keto form to the more favored cyclohexane *trans* configuration followed by relactonization (Scheme 9). The β-*cis*-**9a**–**c** and the β-*trans*-**9a**–**c** epimers were easily separated by flash column, and the β-*cis*-**9a**–**c** could again be epimerized to a 2:1 mixture of β-*trans*-**9a**–**c** and β-*cis*-**9a**–**c** through treatment with HCl in water/THF at 65 °C. The lactols were isolated by extraction with CH_2Cl_2. The CH_2Cl_2 solution was partially concentrated, and the resulting solution was treated with acetic anhydride to promote ring opening of the lactol to give the ketones **10a**–**c**. The excess amount of acetic anhydride was quenched by the addition of methanol before the reaction mixture was treated with tosyl hydrazide in AcOH/MeOH (1:3) to give the corresponding hydrazones (Scheme 10). Any undesired epimer from the previous hydration of enol ether **8** was separated by flash column, and the hydrazones **11a**–**c** were isolated as a single isomer in good to excellent overall yields from amine **8a**–**c** without purification of synthetic intermediates. All reactions from β-ketoamide **2** to the hydrazone intermediate **11** were remarkably clean, and in most cases, no byproducts could be observed in the crude reaction mixtures by ^{1}H NMR spectroscopy. However, it should also be pointed out that the β-*trans*-quinolizidine series was more difficult to handle than the α-*trans*- and β-*cis*-quinolizidine derivatives, in particular during purification by flash column, which is also reflected in the lower isolated yields of these compounds. The entire reaction sequence starting from β-ketoamide **2a**,**b** and α,β-unsaturated aldehyde **1** was also performed without any purification of synthetic intermediates on a multigram scale to give **12b**-α-*trans*-**11a** as a single isomer in 63 % overall yield and **11b**-α-*trans*-**11a**,**b** and **11b**-β-*cis*-**11a**,**b** as a 1:1 mixture in 62 % combined overall yield (Scheme 11).



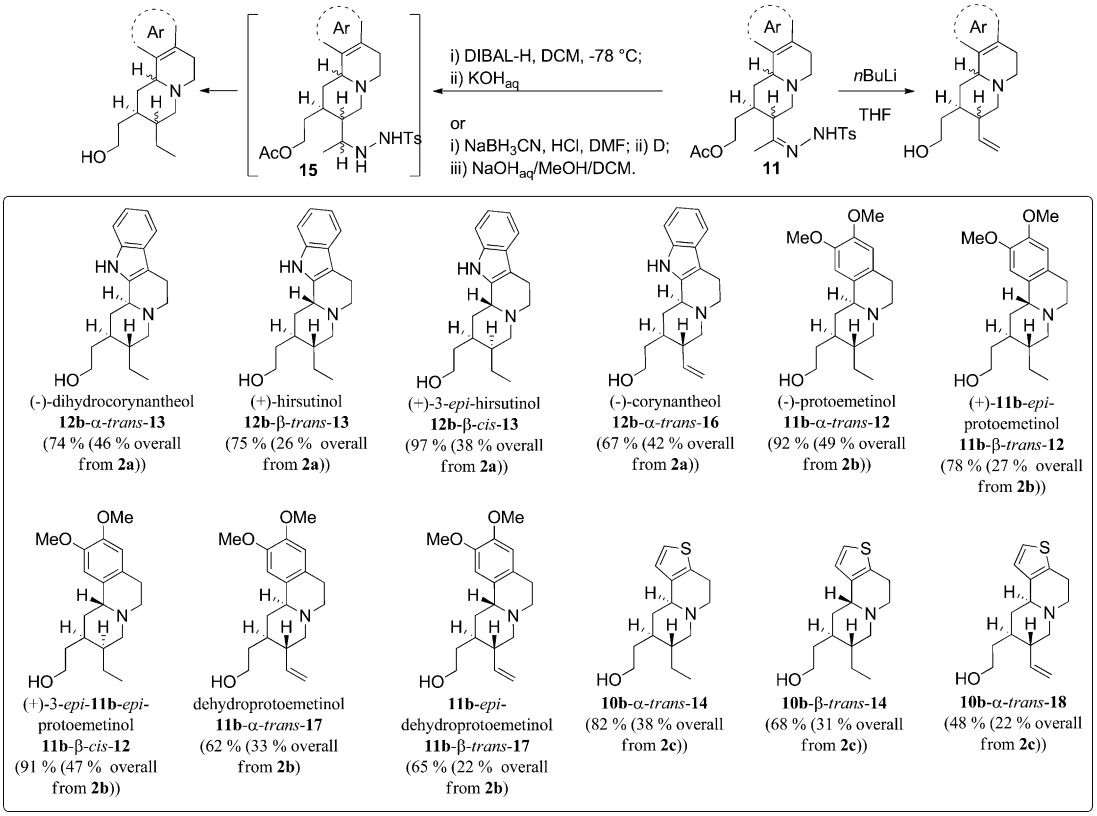
Scheme 10. Stereodivergent syntheses of hydrazone intermediates **11a**–**c**.

Applications in total synthesis: We decided to proceed through the hydrazone intermediate because from here we have a choice of full reduction to the saturated C^3 alkyl chain or partial reduction under Shapiro conditions to give the C^3 vinyl group. The full reduction of benzo[*a*]quinolizidine-hydrazones α-*trans*-**11b** and β-*cis*-**11b** to the ethyl group and the simultaneous reductive cleavage of the acetate moiety was accomplished by using diisobutylaluminium



Scheme 11. Multigram syntheses of hydrazone intermediates **11a**,**b**.

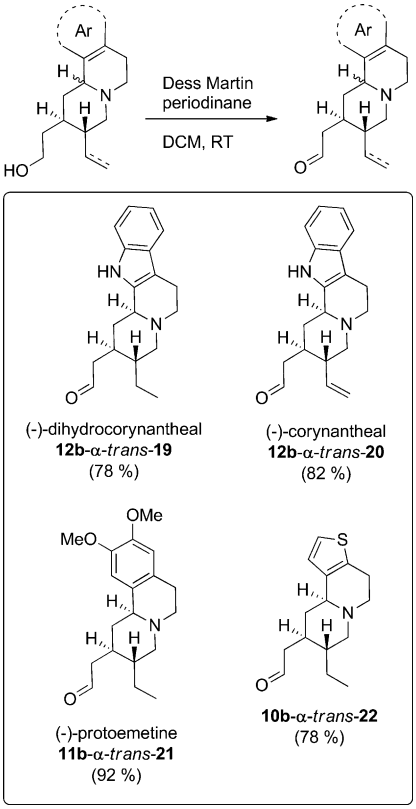
hydride (DIBAL-H). Full consumption of the starting material was observed after 10 min at −78 °C in a clean and high-yielding reaction to give the natural product (−)-protoemetinol (**11b**-α-*trans*-**12**) in 92% yield from **11b**-α-*trans*-**11b** and 49% overall yield from β-ketoamide **2b**. In the same manner, the analogues 3-*epi*-**11b**-*epi*-protoemetinol (**11b**-β-*cis*-**12**), 3-*epi*-hirsutinol (**12b**-β-*cis*-**13**), and thieno[3,2-*a*]quinolizidine (**10b**-α-*trans*-**14**) were prepared in high yields (Scheme 12). On the other hand, DIBAL-H reduction of benzo[*a*]- and thieno[3,2-*a*]quinolizidine-hydrazones α-*trans*-**11b**,**c** was sluggish and after 10 min reaction time only the intermediate hydrazine **15** could be isolated, along with several unidentified byproducts. Prolonged reaction time at elevated temperature (DIBAL-H, 3 h, RT) slowly decomposed the hydrazine intermediate to the product in low yields. The hydrazine intermediate **15** was remarkably stable and could be isolated before it was thermally decomposed at 70 °C to the desired product in low yields. The α-*trans*- and β-*trans*-indolo[2,3-*a*]quinolizidine hydrazones **11a** also reacted with poor selectivity with DIBAL-H and gave low yields and mixtures of product and byproducts. After screening of different reducing agents we found that $NaBH_3CN$ in the presence of 3 equivalents of HCl cleanly reduced indolo[2,3-*a*]quinolizidine hydrazones **12b**-α-*trans*-**11a** and **12b**-β-*trans*-**11a**, benzo[*a*]- and thieno[3,2-*a*]quinolizidine hydrazones β-*trans*-**11b**,**c** to the corresponding hydrazines **15**. The intermediate hydrazines **15** were isolated by extraction and heated in DMF (100 °C) to decompose the hydrazine intermediate, followed by addition of KOH_{aq}/methanol/CH_2Cl_2 to hydrolyze the acetate group, thereby giving the natural product (−)-dihydrocorynantheol (**12b**-α-*trans*-**13**) and (+)-hirsutinol (**12b**-β-*trans*-**13**) as well as the analogues (+)-**11b**-*epi*-protoemetinol (**11b**-β-*trans*-**12**) and thieno[3,2-*a*]quinolizidine **10b**-β-*trans*-**14** in good overall yields (Scheme 12). As previously mentioned, the hydrazone



Scheme 12. Preparation of a series of natural products, their analogues and epimers through full and partial hydrazone reduction.

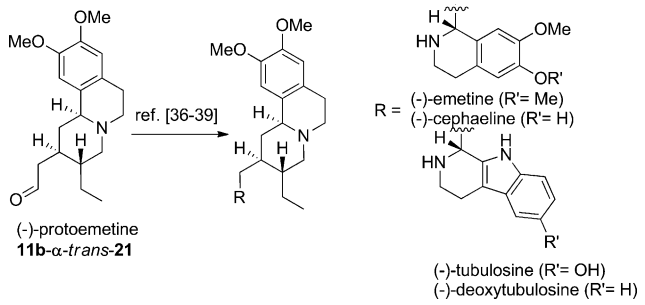
moiety also provides access to a vinyl group at the C^3 position through partial reduction under Shapiro conditions. Thus, treatment of hydrazones α-*trans*-**11** and β-*trans*-**11** with *n*BuLi resulted in the elimination of the hydrazone and deacetylation to provide access to the natural product (−)-corynantheol (**12b**-α-*trans*-**16**) and the analogues dehydroprotoemetinol (**11b**-α-*trans*-**17**), **11b**-*epi*-dehydroprotoemetinol (**11b**-β-*trans*-**17**), and thieno[3,2-*a*]quinolizidine **10b**-α-*trans*-**18** in moderate to good yields (Scheme 12).

The hydroxyquinolizidines were smoothly oxidized by using Dess–Martin periodinane to give the naturally occurring alkaloids (−)-dihydrocorynantheal (**12b**-α-*trans*-**19**), (−)-corynantheal (**12b**-α-*trans*-**20**) and (−)-protoemetine (**11b**-α-*trans*-**21**), and the analogue thieno[3,2-*a*]quinolizidine **10b**-α-*trans*-**22** in overall high yields (Scheme 13). (−)-

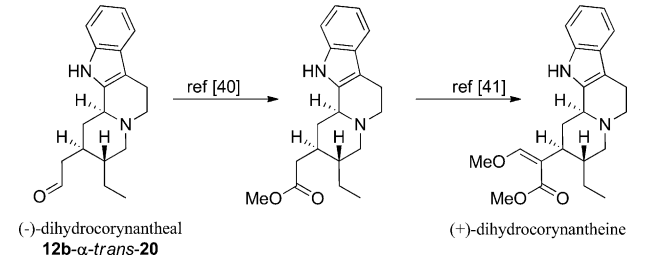


Scheme 13. Natural product synthesis.

Protoemetine occupies a key position among the ipecac alkaloids since it is considered to be an intermediate in the biogenesis of emetine and several related alkaloids.[35] Thus, the quinolizidine aldehydes **19**–**22** are useful synthetic precursors for further transformation into a broad variety of quinolizidine natural products of higher structural complexity. For example, the methodology described here represents an efficient formal synthesis of (−)-emetine,[36] (−)-cephaeline,[36,37] (−)-tubulosine,[38] and (−)-deoxytubulosine[39] through the Pictet–Spengler annulation of (−)-protoemetine **21** with 3,4-dimethoxyphenylethylamine, *O*-methyldopamine, serotonin, and tryptamine, respectively (Scheme 14). Furthermore, Jones oxidation of dihydrocorynantheal **19** in methanol gives the corresponding methyl ester;[40] subsequent formylation and methylation provides an efficient formal synthesis of (+)-dihydrocorynantheine (Scheme 15).[41] The same approach should also provide access to hirsutine and corynantheine from hirsutinol and corynantheal.

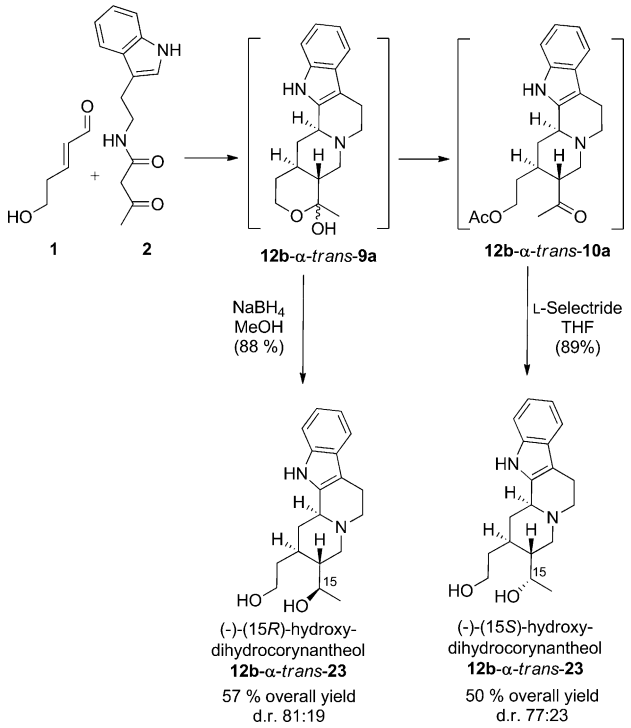


Scheme 14. The formal synthesis of (−)-emetine, cephaeline, (−)-tubulosine, and (−)-deoxytubulosine from (−)-protoemetine **11b**-α-trans-**21**.



Scheme 15. The formal synthesis of (+)-dihydrocorynantheine from (−)-dihydrocorynantheal **12b**-α-*trans*-**19**.

This methodology was also applied in the protecting-group-free total synthesis of (−)-(15*S*)-hydroxydihydrocorynantheol **12b**-α-*trans*-**23**, an alkaloid isolated in 1999 from an endemic tree of Puerto Rico, *Antirhea portoricensis* (Rubiaceae).[42] Lactol **12b**-α-*trans*-**9a** was prepared without purification of intermediates and the crude compound was dissolved in methanol/CH_2Cl_2 and directly reduced with $NaBH_4$ to give an 81:19 mixture of diols in high yields (Scheme 16). By comparing the ^1H NMR spectroscopic data of the major isomer with literature data, we were able to conclude that this was the nonnatural epimer (15*R*)-hydroxydihydrocorynantheol **12b**-α-*trans*-**23**. However, opening of the lactol **12b**-α-*trans*-**9** to the ketone **12b**-α-*trans*-**10** and subsequent reduction by using L-Selectride gave the natural product (−)-(15*S*)-hydroxydihydrocorynantheol **12b**-α-*trans*-**23** with 77:23 diastereoselectivity and 50% combined overall yield from β-ketoamide **2a**.[43]



Scheme 16. Purification and protecting group free total synthesis of natural product (−)-(15*S*)-hydroxydihydrocorynantheol **12b**-α-*trans*-**23** and its epimer (15*R*)-hydroxydihydrocorynantheol.

Conclusion

We have described the development of a highly efficient and enantioselective synthetic strategy that allows for access to a broad number of optically active quinolizidine alkaloids of the corynantheine and ipecac families on a multigram scale. The optical activity is introduced by asymmetric catalysis that starts from easily available nonchiral starting materials, and the following two stereocenters are introduced through diastereodivergent reactions. By employing diastereodivergent steps, selective access to 3 out of 4 possible optically active diastereomers can be realized from common starting materials by using the same synthetic strategy. The focus during the development of this strategy has been on efficiency, and the majority of our attention has been devoted to excluding protection groups and finding reaction conditions compatible with a limited number of isolation and purification steps. Most of the reaction steps are extremely high yielding and the potential of this methodology in natural product synthesis is demonstrated by the total synthesis of (−)-dihydrocorynantheol in 47% overall yield, (−)-protoemetinol in 49% overall yield, and (−)-corynantheol in 42% overall yield from easy accessible α,β-unsaturated aldehyde **1** and β-ketoamide **2**. Furthermore, this methodology also provides easy access to an array of epimers and analogues not accessible through synthetic elaboration of naturally occurring alkaloids, which is exemplified by the synthesis of the thieno[3,2-*a*]quinolizidine natural product analogues as well as the synthesis of the β-*cis*-quinolizidine series. This synthetic strategy also provides easy access to the natural products (−)-dihydrocorynantheal, (−)-corynantheal, (−)-protoemetine, and different analogues thereof in high overall yields. We also describe the total synthesis of (−)-(15*S*)-hydroxydihydrocorynantheol and the formal synthesis of (−)-emetine, (−)-cephaeline, (−)-tubulosine, (−)-deoxytubulosine, and (+)-dihydrocorynantheine. The major benefits of this strategy are the easily available starting materials, common synthetic strategy, stereodivergent reaction steps, omission of protection groups, and limited isolations and purifications of reaction intermediates. Due to efficiency, product diversity, and operational simplicity, this protocol has the potential to find important uses in natural product synthesis, biochemistry, and pharmaceutical science.

Experimental Section

Purification-free multigram preparation of hydrazone 12b-α-*trans*-11a: β-Ketoamide **2a** (2.44 g, 10 mmol) and *R* catalyst **3** (650 mg, 2 mmol) were dissolved in CH_2Cl_2 (10 mL). 5-Hydroxyl-pentaldehyde **1** (1.20 g, 1.2 mmol) was added to this solution, and the resulting reaction mixture was stirred until a white or white/brown precipitate was formed that indicated full conversion. Acetyl chloride (100 mmol, 7.10 mL) was added, and the mixture was stirred overnight at room temperature. The reaction was quenched by addition of saturated $NaHCO_{3(aq)}$, and the water phase was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL) followed by addition of di-*tert*-butylpyridine (5.70 g, 35 mmol) and $Et_3O{\cdot}BF_4$ (3.80 g, 25 mmol). After 4 h, CH_2Cl_2 was removed under vacuum, and the residue was redissolved in methanol (150 mL) and cooled to 0 °C. $NaBH_4$ (2.30 g, 60 mmol) was added in small portions, and the resulting mixture was stirred for 1 h at room temperature. Methanol was removed under vacuum and the residue was dissolved in THF (100 mL) and 2 M $HCl_{(aq)}$ (100 mL). The mixture was stirred overnight before being quenched with saturated $NaHCO_3$ and NaOH (10 mL, 5% aqueous solution). The water phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4). CH_2Cl_2 was removed under vacuum until approximately 100 mL remained. Pyridine (8.0 g, 100 mmol), 4-dimethylaminopyridine (DMAP; 30 mg, 0.2 mmol), and acetic anhydride (10 g, 100 mmol) were added to this solution in turn. The reaction was left for 4 h at room temperature before saturated $NaHCO_3$ was added. The water phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4). The solvent was removed, then the residue was dissolved in methanol (120 mL) and acetic acid (40 mL) followed by the addition of tosylhydrazide (3.72 g, 20 mmol). The reaction was stirred overnight at room temperature before being quenched with saturated $NaHCO_3$. The water phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified with column chromatography to give **12b**-α-*trans*-**11a** as a yellow solid (2.77 g, overall yield: 53%).

(−)-Dihydrocorynantheol 12b-α-*trans*-15: HCl (3 equiv, 1 M in Et_2O) was added dropwise at 0 °C to a solution of the hydrazone **12b**-α-*trans*-**11a** and $NaBH_3CN$ (2.2 equiv) in DMF ($c = 0.1$ M). The resulting mixture was stirred at room temperature overnight and quenched with $Na_2CO_{3(aq)}$ (2 M). The water phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a solution of the crude tosylhydrazine in DMF. The DMF solution was heated at 100 °C for 45 min before being cooled to room temperature. CH_2Cl_2 (10 mL mmol^{-1}), MeOH (10 mL mmol^{-1}), and $KOH_{(aq)}$ (1 M, 10 mL mmol^{-1}) were added, and the resulting mixture was stirred vigorously for 2 h before being dispersed between CH_2Cl_2 and water. The water phase was extracted with CH_2Cl_2, and the combined organic phases were dried (Na_2SO_4), filtered, and concentrated

under reduced pressure. The crude product was purified by flash chromatography (EtOAc/MeOH) to give the title compound in 74% overall yield. $[\alpha]_D^{20} = -13.5$ ($c = 0.004$ in $CDCl_3$) (lit: $[\alpha]_D^{20} = -20.4$ ($c = 0.25$ in $CDCl_3$)). All characterization data was in accordance with those previously reported.[44,45]

(−)-Corynantheol 12b-α-*trans*-16: The hydrazone compound **12b**-α-*trans*-**11a** was dissolved in anhydrous THF ($c = 0.1$ M) under nitrogen atmosphere and cooled down to −78 °C. *n*BuLi (5 equiv, 2.3 M in hexane) was added dropwise to this solution. During the addition, the reaction mixture turned from yellow to brown, and the resulting solution was allowed to slowly reach room temperature and stirred overnight. Brine (5 mL) was added to quench the reaction and the water phase was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/MeOH) to give the title compound in 67% yield according to the general procedure described above. $[\alpha]_D^{20} = -65.0°$ ($c = 0.05$ in $CDCl_3$) (lit: $[\alpha]_D^{20} = -61°$). All characterization data were in accordance with those previously reported.[46]

Acknowledgements

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