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Enantioselective Synthesis of (−)-Gilbertine via a Cationic Cascade Cyclization

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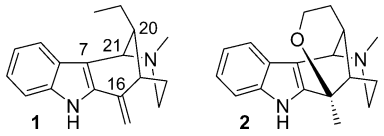
Abstract: Described is the first enantioselective synthesis of (−)-gilbertine (**2**), a member of the uleine-type family, and the determination of the absolute configuration of this natural product is reported. The key step employs a cationic cascade reaction for a tetrahydropyrane and piperidine ring formation and the construction of the pentacyclic framework in one step. The synthetic strategy utilizes the Shibasaki reaction to build up the first stereogenic center. A formylation reaction of a 3-substituted cyclohexanone derivative was achieved, giving only the desired regioisomer. The Japp−Klingemann Fischer indole protocol was used successfully as a convergent synthetic approach for the construction of the desired tetrahydrocarbazole (**20**). Furthermore, an unexpected behavior of this 2,3-disubstituted cyclohexanone derivative during an epimerization process was investigated, resulting in different chemical behavior of the enantiomers and the racemate. The diastereomeric resolution was achieved via the cationic cascade reaction, demonstrating the versatility of this approach. Significantly, the synthetic 17-step sequence was easy to execute, giving (−)-gilbertine in 5.5% overall yield.

Introduction

Uleine-type indole alkaloids such as uleine (**1**) have been of synthetic interest over the past few decades (Chart 1).[1] There have been a number of reports for racemic and enantioselective syntheses of uleine and *epi*-uleine.[2] However, syntheses of *epi*-uleine are predominant in these series as a result of the electrophilic C-21−C-7 cyclization approach.[3] The iminium ion used for this final ring formation is subjected to an imine−enamine tautomerization resulting in an epimerization of the ethyl group at C-20. Steric discrimination in the event of cyclization leads to the epi derivative as the major product. This is the main reason that the synthesis of the natural product is more problematic than it is for the epi series. Our synthetic approach to the uleine framework excludes epimer formation by employing a nucleophilic N−C bond formation at C-21. Herein we demonstrate the application of this strategy in the first enantioselective synthesis of (−)-gilbertine (**2**), a member of the uleine family.

Chart 1



Gilbertine was first isolated in 1982 from the *Aspidosperma gilbertii* (A. P. Duarte), as well as uleine and a large number of related indole alkaloids.[4] The compact pentacyclic framework and the additional stereogenic center at C-16 are unusual structural features compared to the other members of the uleine alkaloid group, which has resulted in gilbertine remaining a synthetic challenge during the last 20 years. The following enantioselective synthesis allows the determination of the absolute configuration of the natural product and employs a cationic domino process to build up the pentacyclic framework in one step.

Synthetic Strategy

Our strategy to the *Aspidosperma* pentacycle was based on a cationic cascade reaction of the tetrahydrocarbazole **5**.[2e] It was envisaged that **5** could give, upon treatment with acid, a carbocation that would rearrange through intermediates **3** and **4**, allowing the generation of the pseudo-benzylic carbocation required for the final tetrahydropyrane ring formation. One important requirement for the generation of the pseudo-benzylic carbocation would be that the *N*-acetoxy group perform as a leaving group in intermediate **4**.

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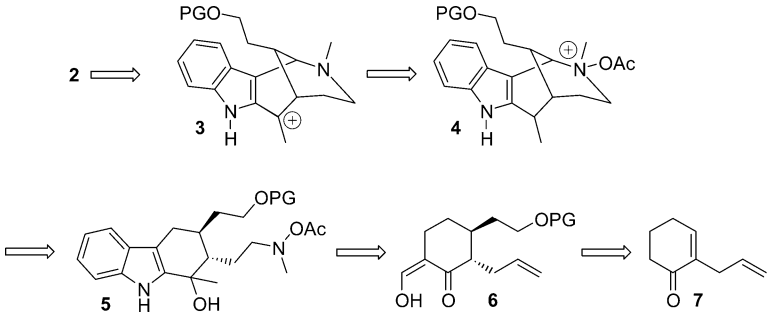
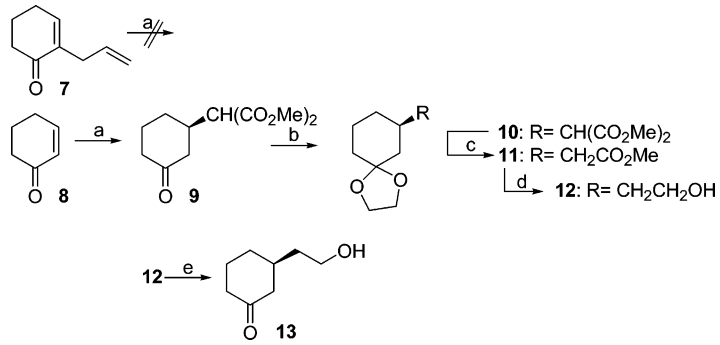
10.1021/ja0399021 CCC: $27.50

Scheme 1. Retrosynthesis



Scheme 2 [a]



[a] Reagents and conditions: (a) 1 mol % (R-AlB), KO^{t}Bu, dimethylmalonate, THF, 96%, >99% ee; (b) ethylene glycol, *p*TSOH, reflux, 99%; (c) DABCO, H_2O, toluene, reflux, 66%; (d) LAH, Et_2O, reflux, 97%; (e) CH_3CN, H_2O, 1 N HCl, rt, 91%.

Tetrahydrocarbazole **5** could be synthesized by a convergent approach by use of the Japp−Klingemann[5] Fischer indole[6] synthesis, which would predict the highly substituted cyclohexanone **6** addressing two of the four stereogenic centers (see Scheme 1). The allyl moiety in **6** would allow the introduction of the hydroxylamine side chain via an oxidative cleavage[7] reductive amination[8] protocol. The carbonyl functionality would be suitable for the introduction of the methyl group, and simple acetylation should give the cyclization precursor **5**.

The Shibasaki asymmetric Michael addition could introduce the hydroxyethyl side chain by use of 2-allylcyclohexenone **7**, which could be easily prepared from *o*-anisic acid under Birch conditions on a large scale,[9] and dimethylmalonate as a commercially available starting material, allowing the synthesis on a molar scale.[10a] By use of Corey's protocol for the introduction of a formyl moiety, the highly substituted cyclohexanone derivative **6** should be straightforwardly synthesized.[11] The protection group (PG) should be easily cleaved under the acidic cyclization conditions in the last step of the synthesis, but it should be stable under the acidic Fischer cyclization conditions.

Results and Discussion

Synthesis of Gilbertine. The Michael reaction with cyclohexenone derivative **7** was not successful; only starting material was isolated (Scheme 2). Evaluation of this reaction led to the conclusion that **7** is not a Michael acceptor for the Shibasaki reaction or any other base-catalyzed reaction conditions. Since the Shibasaki reaction delivers high yields and excellent enantiomeric excess, it was envisaged to introduce the allyl moiety at a later step in the synthesis (Scheme 3). For the optimization of the entire procedures, especially the introduction of the allyl moiety, the racemate was synthesized in a parallel manner. The asymmetric Michael addition of dimethyl malonate with cyclohexenone in the presence of R-AlB was achieved in 96% yield with an excess of >99% ee, achieved by recrystallization.[10b] To avoid a retro-Michael process under decarboxylation conditions, ketone **9** was protected as a cyclic ketal **10**. The Krapcho decarboxylation[12] procedure was replaced by a milder procedure with DABCO in toluene and water, which afforded **11** in 66% yield. LAH reduction of the methyl ester and deketalization with 1 N HCl_{aq} in acetonitrile gave rise to hydroxylethylcyclohexanone **13**. These reactions were easily carried out on a molar scale and it is noteworthy that all intermediates could be purified by distillation or used without purification.

At the planning stage of the synthesis it was envisaged that a bulky protecting group (PG, Scheme 1) could effect the formylation of hydroxyethylcyclohexanone in a regioselective manner. This formylation[11] would allow the introduction of the allyl side chain by bisanion alkylation,[13] which would be stereoselectively influenced by the protected hydroxyethyl side chain giving rise to the favored trans diastereomer. Therefore we investigated the influence of the TPS protecting group, which could be introduced in a 97% yield (Scheme 3). This TPS ether

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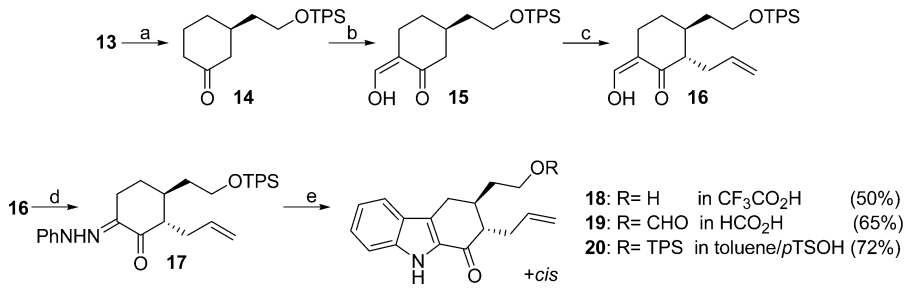
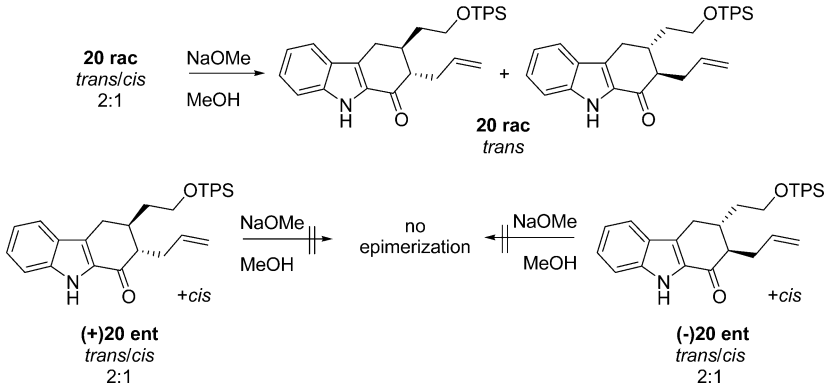
Scheme 3 [a]



[a] Reagents and conditions: (a) imidazole, TBDPSCl, DMF, rt, 97%; (b) HCO_2Et, NaH, THF, rt, 78%; (c) LDA, THF, −78 °C, and then allyl bromide, −78 °C to room temperature, 75%; (d) aniline, HCl concd, $NaNO_2$, H_2O, 0 °C, and then NaOAc, addition of **16** in THF, 0 °C, 65−90%; (e) (1) CF_3CO_2H, 80 °C, 50%, (2) HCO_2H, 80 °C, 65%, (3) *p*TSOH, toluene, reflux, 72%.

Scheme 4. Equilibration of the Allyl Moiety Adjacent to the Carbonyl Group[a]



[a] Detection of the diastereomers and enantiomers was achieved by chiral HPLC, Chiralpak OD, and ^1H NMR spectroscopy. Solvent system: hexane/2-propanol 95:5, flow 1 mL/min., retention time(minutes): **20(S)** trans diastereomer, 11.07; **20(S)** cis diastereomer, 9.99; **20(R)** trans diastereomer, 12.01; **20(R)** cis diastereomer, 8.41.

moiety of **14** should fulfill the following demands: (1) it should direct the formylation reaction, (2) it should be stable under acidic Fischer indole synthesis, and (3) it should be cleavable during the acidic cyclization procedure in the last synthetic step. Gratifyingly, the regioselective and diastereoselective formylation was achieved in 89% yield on a 0.2 g scale, whereas a scale-up to 10 g decreased the yield to 78%; however, only the desired regioisomer was detected by ^1H NMR. Bisanion formation and allylation afforded the highly substituted ketone **16** in 75% yield. For the Japp−Klingemann reaction, we utilized a modified protocol, in which the strongly acidic diazonium salt solution was initially treated with sodium acetate and then **16**, which increased the yield from 10% to 65−90% yield.

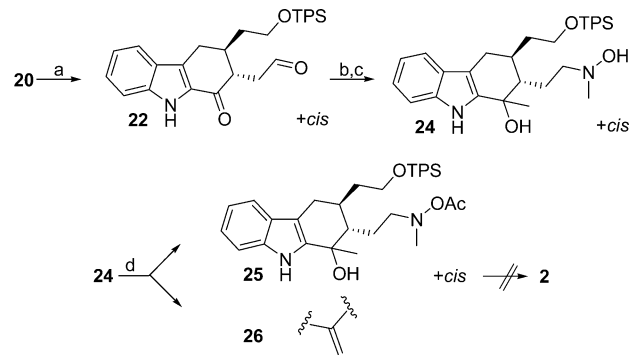
Which products were isolated from the Fischer indole reaction depended strongly on both the solvent and the pK_a of the acid promoter. Pivalic acid gave no conversion, and formic acid treatment resulted in deprotection of the alcohol and formation of the formylester **19**, whereas trifluoracetic acid gave the deprotected hydroxyindole **18**. *p*-Toluenesulfonic acid (*p*TSOH) in THF gave only decomposition; however, in toluene the desired indole **20** could be isolated in 72% yield. Unfortunately, the acidic conditions resulted in a loss of the trans configuration and a 2:1 (trans:cis) diastereomeric mixture of **20** was formed and determined by ^1H NMR.

As mentioned earlier, the synthesis of **20** was performed in the racemic and the enantiomeric pure form. An equilibration of the racemate **20rac** with sodium methoxide in methanol resulted in the expected thermodynamic favored trans configuration. Surprisingly, the same reaction conditions used for the enantiomeric pure form **(−)-20ent** resulted in no change of the diastereomeric ratio; even after treatment for 1 month, no deviation from the equilibrium diastereomeric ratio was observed (Scheme 4).

We decided to further investigate this rather rare appearing phenomenon of different chemical behavior of the racemate and the enantiomeric pure form. Therefore, we synthesized **(+)-20ent** to have the series complete for experimental and analytical data. All experiments were carried out under the exact same reaction conditions in a parallel manner. In the racemate **20rac** a precipitate was formed during the epimerization process and this showed the desired substitution pattern, whereas no change was observed in **(−)-** and **(+)-20ent**. Deuterium exchange experiments clearly demonstrated that enolate formation was achieved in all cases. Therefore, we propose that the precipitation process is the reason for the epimerization, which is evidenced by the following experiment. The equilibrated racemate *trans*-**20rac** was suspended and treated under diluted conditions, when all the solid material was dissolved and the expected reequilibration to the equilibrium diastereomeric ratio occurred after 2 weeks. We further proposed that the reequilibration process of *trans*-**20rac** must also be achieved under acidic conditions. Treatment of a solution of equilibrated **20rac** in boiling toluene with *p*TsOH showed rapid reequilibration to a 2:1 ratio with concurrent cleavage of the silyl ether after 10 min.

These experiments provide evidence for complex formation of ***n*·[(+)-20-*trans*·(−)-20-*trans*],** which is less soluble than the cis isomers; however, this complex formation is strictly dependent on concentration. Furthermore, if precipitation via complex formation is the reason for the epimerization, we would

Scheme 5 [a]



[a] Reagents and conditions: (a) (1) OsO_4, NMO, acetone/water, rt, 90%, (2) $Pb(OAc)_4$, K_2CO_3, toluene, rt, 95%; (b) $CH_3NOH{\cdot}HCl$, $NaBH_3CN$, 2-propanol/water, rt, 90%; (c) MeLi, THF, −60 °C to room temperature, 82%; (d) Ac_2O, pyridine, rt, 75%.

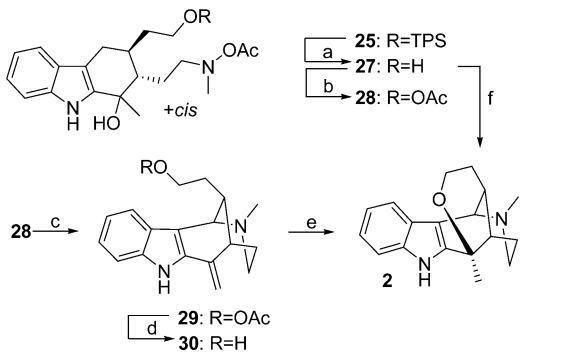
expect that the addition of the same amount of **(+)-20ent** to the **(−)-20ent** in solution would result in a precipitation of this complex with the desired trans substitution pattern, which could have been observed. All experiments indicated that there is no energetic preference for the trans-substituted derivative. To further confirm the experimental data, we have calculated the stabilization energies of the stereoisomers and an energy difference of 4.18 kJ/mol was found, a value too small for a differentiation of the stereoisomers.[14] Nevertheless, we predicted that separation of the diastereomers will be achieved by the final cyclization process, where only the trans diastereomer is capable of forming the piperidine ring leading to (−)-gilbertine. Since an equilibration of **25** was not expected during the cascade reaction conditions, we considered the loss of the cis diastereomer. Due to steric hindrance in the case of the cis diastereomer, the cyclization process is disabled at the step of the piperidine ring formation and the reaction cascade cannot proceed further. Therefore, we accomplished the synthesis with the diastereomeric mixture as shown in Scheme 5.

Oxidative cleavage of **20** gave rise to the aldehyde **22** in 86% yield in a two-step procedure. Reductive amination was accomplished with cyanoborohydride and *N*-methylhydroxylamine in 90% yield. Subsequent addition of methyllithium gave rise to alcohol **24** in 82% yield. To provide the leaving groups for the final cyclization reaction, subsequent peracetylation of the hydroxy groups gave rise to the cyclization precursor **25**. Elimination of the tertiary acetate was observed as a side reaction, but the resulting double bond should also be a source for the acid-induced formation of the tertiary carbocation.

The cyclization was initially carried out in formic acid and a 1:1 mixture of dichloromethane/trifluoroacetic acid, but unfortunately no natural product was formed and complete decomposition was observed. We proposed that the bulky TPS group could hinder the process and therefore the reaction was carried out in a mixture of aqueous HCl in THF in order to ensure cleavage of the silyl ether, resulting in decomposition. The precursor of the known uleine cascade reaction[2e] differs only in the additional hydroxy group, and therefore a change of the protection group could indicate if the cascade reaction can take place or if the cis diastereomer interacts with the cascade intermediates. The TPS group was removed in 93% yield and the hydroxy group was protected as an acetate (Scheme 6).

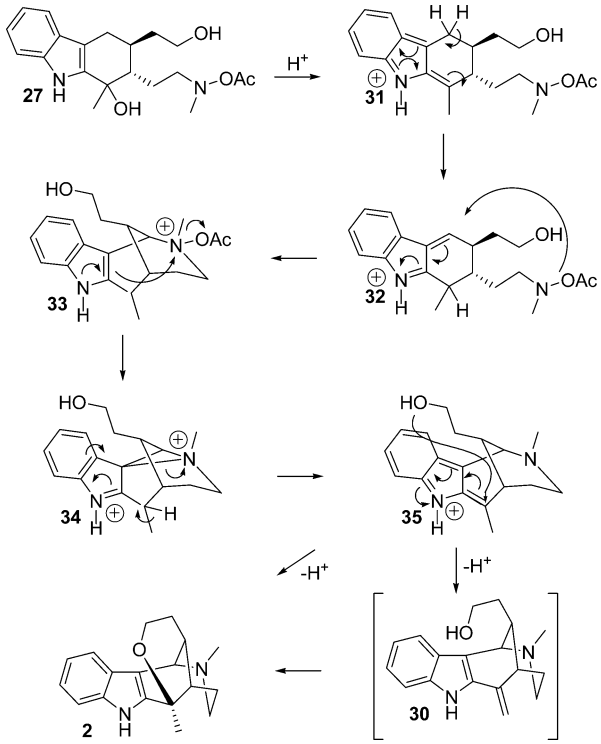
(14) See Supporting Information (S17).

Scheme 6 [a]



[a] Reagents and conditions: (a) TBAF, THF, rt, 93%; (b) Ac_2O, pyridine, rt, directly used in next step; (c) HCO_2H, rt, directly used in next step; (d) K_2CO_3, MeOH, rt, 100%, directly used in next step; (e) CF_3CO_2H, rt, 50% overall yield; (f) CF_3CO_2H, 61%.

Scheme 7



Treatment with formic acid resulted in the formation of the desired hydroxyuleine acetate **29** in 50% yield. The acetate was removed with K_2CO_3 in methanol and hydroxyuleine **30** was converted quantitatively to gilbertine in the dichloromethane/trifluoracetic acid solvent mixture used previously. On the basis of this pathway, we thought that the unprotected tetrahydrocarbazole **27** could give gilbertine directly and the cyclization occurred in 61% yield. Gratifyingly, spectral and analytical data for **2** were comparable with those reported in the literature [see ref 4; reported $[\alpha]^{20}_D = -149$ ($CHCl_3$), measured: $[\alpha]^{20}_D = -143.8$ ($c = 0.08$, $CHCl_3$)]. The comparison of both values confirms the configuration of the natural product. On the basis of the enantioselective Michael addition (Shibasaki procedure), we assign the absolute configuration of (−)-gilbertine as shown in Scheme 1.

Mechanism of the Cationic Cascade Reaction. We propose the mechanism of the cyclization outlined in Scheme 7. Loss

of the tertiary alcohol or protonation of the exomethylene double bond affords a carbocation, which tautomerizes to the iminiumsalt **32**. Nucleophilic attack on the aza analogue Michael system by the NOAc moiety gives rise to the ammonium acetate **33**. An intramolecular substitution of the acetate gives rise to the azacyclopropane derivative **34**, which yields the iminium ion **35** after fragmentation. Finally, after **35** tautomerizes to the indole moiety, the tertiary cation is trapped intramolecularly by the hydroxy group. Elimination could also afford hydroxyuleine, which would be in equilibrium with gilbertine in acidic medium. However, only gilbertine **2** was isolated.

The possible intramolecular trapping of the initial tertiary cation by the hydroxy group may occur; however, it would be expected to be a reversible process under protic conditions and it is believed that the cation release over the indole moiety occurs faster than a S_N1 process. Furthermore, reaction monitoring indicated the formation of hydroxyuleine **30** as an intermediate, underlining the proposed reaction pathway. Experiments with uleine derivatives have shown further evidence of the proposed mechanism.[15]

Conclusion

We have achieved the first enantioselective synthesis of (−)-gilbertine, a member of the *Aspidosperma* alkaloids, in a 17-step sequence with a 5.5% overall yield. The employment of the cationic cascade reaction has shown to be highly stereoselective and furthermore useful for an additional diasteromeric resolution. Further studies to synthesize other members of the *Aspidosperma* alkaloid group in an epimeric pure form are in progress.

Supporting Information Available: Experimental procedures and spectral data (PDF). This information is available free of charge via the Internet at http://pubs.acs.org.

JA0399021

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