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Synthesis of (+)-Centrolobine and Its Analogues by Using Acyl Anion Chemistry

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A new route based on the use of acyl anion chemistry was developed for the synthesis of (+)-centrolobine and its analogues. Acid-catalyzed benzylic cation initiated cyclization was the key step in the stereoselective formation of the *cis*-2,6-disubstituted tetrahydropyran ring. The developed methodology was applied to the synthesis of (+)-centrolobine analogues containing electron-donating substituents in the aryl rings.

Introduction

Diarylheptanoids, a group of natural products characterized by the presence of two aromatic rings across the termini of a seven carbon atom chain, have attracted intense interest from medicinal and synthetic chemists because of their wide-ranging biological activities.[1–3] Among diarylheptanoids containing a tetrahydropyran (THP) ring, (–)-centrolobine (**1**) and its enantiomer (+)-centrolobine (**2**), in particular, have continued to remain in prominence. There are several syntheses reported for **1**;[4] however, in sharp contrast to **1**, there are limited approaches for the synthesis of **2**.[5] Disconnection envisaging use of an aryl acyl anion for the synthesis of **2** has never been attempted. In light of this fact and the attractive diversity factor associated with varying the aryl residue, we were prompted to explore a new synthetic route based on this disconnection (Figure 1). Presented herein are the results of these efforts, which delivered a successful route to **2** and its analogues.

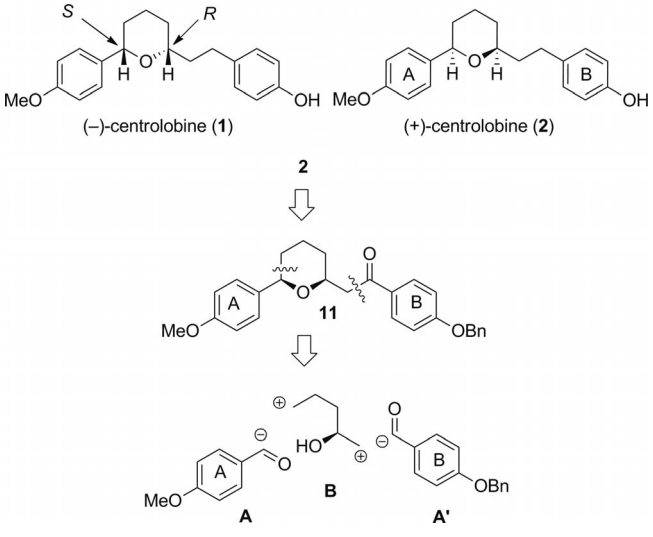

Figure 1. New disconnection for the synthesis of (+)-centrolobine (**2**).

Results and Discussion

Among the several synthetic equivalents available for the acyl anion,[6] we were attracted by the less frequently used α-aminonitriles for the aryl acyl anion synthon **A**/**A′**, because of the simplicity and the convenience involved in their preparation on a multigram scale.[7] Following a literature-known procedure and starting from commercially and abundantly available D-mannitol, bromide **4**[8] was obtained as the requisite synthetic equivalent for five carbon atom electrophilic synthon **B**. α-Aminonitrile **3**[9] underwent clean alkylation with bromide **4** to afford alkylated intermediate **5** as a diastereoisomeric mixture. Without any purification, alkylated intermediate **5** was directly subjected to hydrolysis by using hydrated $CuSO_4$ in aqueous methanol at 60 °C.[10] Clean hydrolysis ensued, which furnished desired aryl ketone **6** in 75% yield (Scheme 1).

To effect benzylic cation initiated cyclization, aryl ketone **6** was reduced to a diastereoisomeric mixture of benzylic alcohol **7** with $NaBH_4$ in methanol. To our satisfaction, upon treatment with *p*-toluenesulfonic acid (*p*TsOH) in methanol, **7** underwent stereoselective cyclization to afford desired *cis*-2,6-disubstituted THP product **8** through deprotection of the ketal followed by intramolecular cyclization initiated by the formation of a benzylic cation under the acidic conditions[4s] (Scheme 2). The cyclization and the formation of **8** was confirmed from a signal at δ = 4.35 ppm

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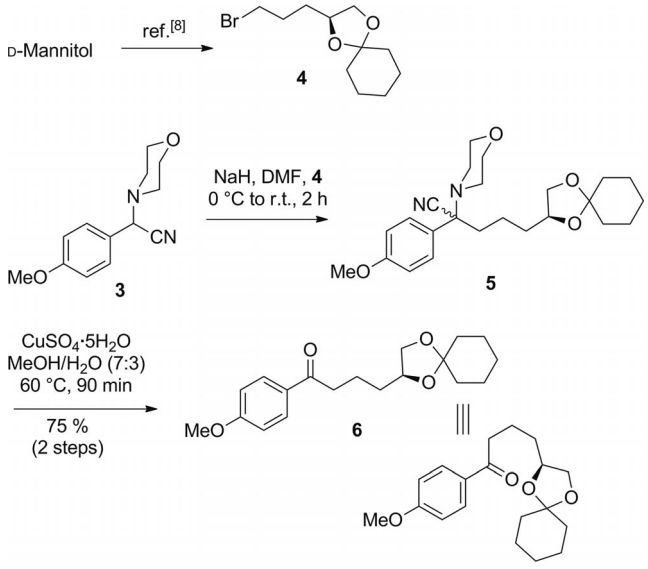
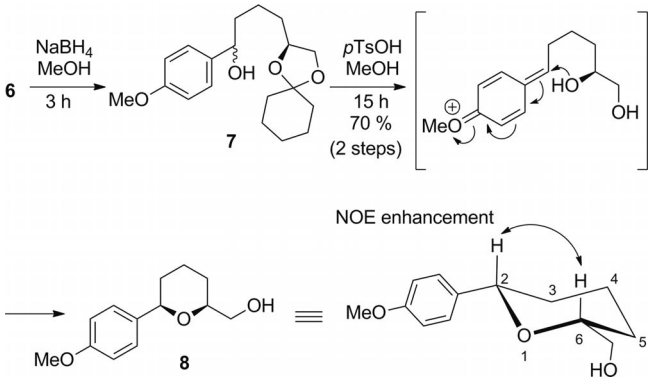


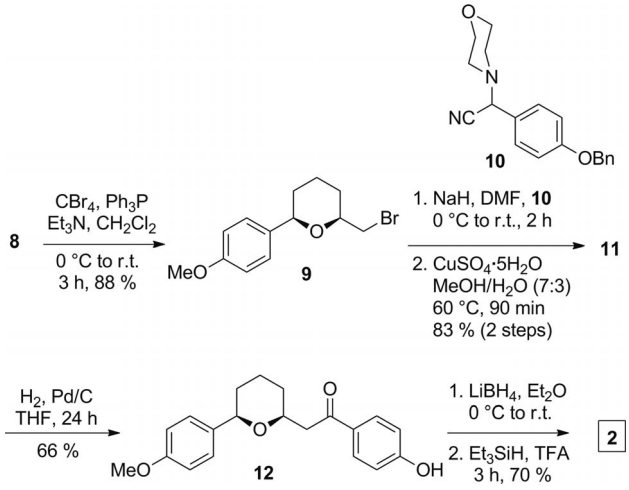
Scheme 1. Synthesis of aryl ketone **6**.

(dd, J = 11.2, 1.6 Hz) in the ^{1}H NMR spectrum, which corresponds to the C-2 benzylic methine proton in the obtained product. Upon irradiation of this peak, an NOE enhancement (3.8%) of the peak at δ = 3.65 ppm corresponding to the methine proton at C-6 in the THP ring was observed, and this demonstrates the close proximity of the C-2 and C-6 protons and hence the *cis* stereochemistry.



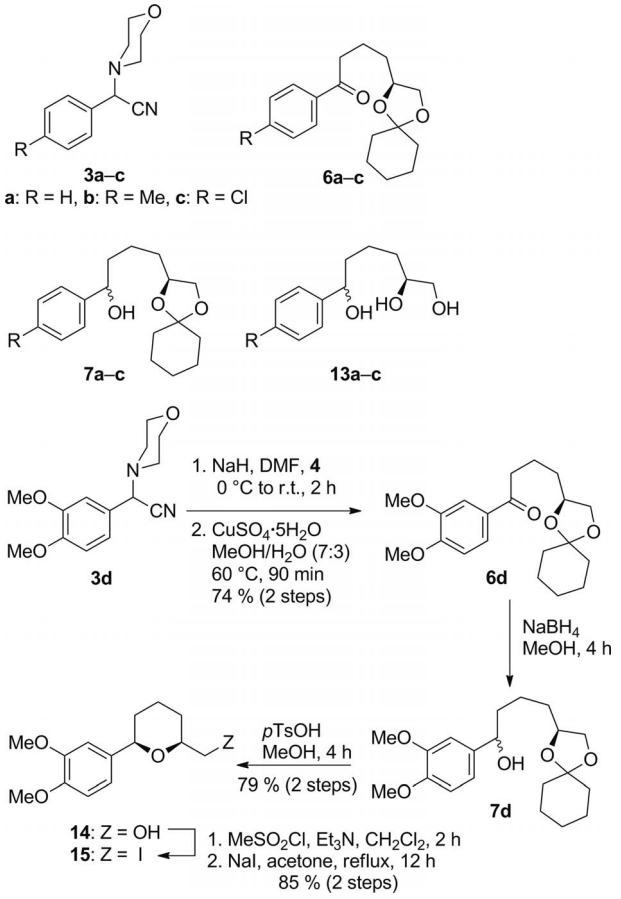
Scheme 2. Stereoselective formation of the THP ring.

To complete the synthesis of **2**, THP alcohol **8** was converted into corresponding bromide **9** with tetrabromomethane and then treated with the carbanion derived from *para*-*O*-benzyl-protected α-aminonitrile **10** for the incorporation of the second aryl residue. The need for final deprotection in addition to the ease with which it could be performed dictated the choice of benzyl ether protected α-aminonitrile **10**. The desired alkylation reaction ensued and subsequent hydrolysis furnished corresponding aryl ketone **11** in 83% yield. With the synthesis of **11**, wherein the carbon framework and aryl residues **A** and **B** of **2** were assembled, the promise of the new strategy based on aryl acyl anion chemistry was fully demonstrated. Simple debenzylation followed by decarbonylation by using a known procedure[5f] afforded target (+)-centrolobine (**2**) in good yield (Scheme 3). All the spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) of compound **2** including the optical rotation value of $[\alpha]_D^{25}$ = +96.6 (c = 0.1, MeOH) {ref.[2c] $[\alpha]_D^{25}$ = +97.5 (c = 0.1, MeOH)} are in agreement with the reported natural product values.



Scheme 3. Synthesis of (+)-centrolobine (**2**). TFA = trifluoroacetic acid.

The successful synthesis of **2** through a novel disconnection on the basis of the use of aryl acyl anion chemistry prompted us to explore the generality of the developed synthetic route. Towards this end, α-aminonitriles **3a**–**c** with varying substituents were prepared to serve as a source for both the aryl residue present in **2** and possibly to provide a diverse array of analogues through various combinations. Although aryl ketones **6a**–**c** were easily prepared in good yields (by using the conditions in Scheme 1), the diastereoisomeric mixture of benzylic alcohols **7a**–**c** obtained after reduction failed to cyclize under the acidic conditions described earlier for the conversion of **7**→**8** in the successful synthesis of **2**. The only reaction that took place under these conditions, even after prolonged stirring, was deketalization, which resulted in triols **13a**–**c**. This was substantiated by the absence of signals for the ketal functionality in the ^{1}H NMR and ^{13}C NMR spectra of the obtained products. The failure of substrates **7a**–**c** to undergo cyclization is probably a result of their inability to form the benzylic cation. The ease of formation of the benzylic cation and the subsequent cyclization in the case of benzylic alcohol **7** are due to stabilization by the *para*-methoxy substituent. To validate this argument, *para*-methoxy-substituted intermediate **7d** was prepared by using **3d** as the starting α-aminonitrile. To our satisfaction, a clean reaction occurred under the acidic conditions described earlier for the conversion of **7**→**8**, and desired *cis*-2,6-disubstituted THP alcohol **14** was furnished in good yield (Scheme 4). The formation of the THP ring in **14** was confirmed by the signal at δ = 4.34 ppm in the ^{1}H NMR spectrum. The exclusive obtainment of the *cis* stereoisomer of **14** was once again confirmed by NOE studies (3.4% enhancement). A simple two-step, high-yielding conversion to iodide **15** set the stage for the incorporation of the second aryl residue as an acyl anion.



Scheme 4. Cyclization to the THP ring with electron-donating substituents.

Upon reaction of **15** with the carbanions generated from α-aminonitriles **3d** and **3** and subsequent hydrolysis of the alkylated products, aryl ketones **16a** and **16b** were obtained, respectively, in good yields. Successful decarbonylation furnished **17a** and **17b**, which are hitherto unknown analogues of (+)-centrolobine (Scheme 5). Similar reactions of bromide **9**, used earlier in the synthesis of **2** (Scheme 3), with the carbanions derived from α-aminonitriles **3d** and **3** provided ready access to analogues **17c** and **17d**, respectively (Scheme 5). The *cis* stereochemistry in final compounds **17a**–**d** was confirmed by NOE studies (3.7, 3.8, 3.8, 4.4% enhancement for **17a**–**d**, respectively). In the case of **17c**, we were fortunate to obtain good-quality crystals for X-ray crystallographic studies, and the single-crystal X-ray diffraction data of **17c**[11] further confirmed the *cis* geometry (Figure 2). The successful synthesis of analogues **17a**–**d** has clearly demonstrated the versatility of the new disconnection and the generality of the developed synthetic route for (+)-centrolobine.

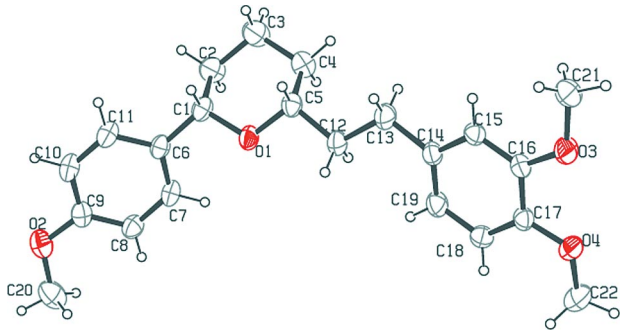


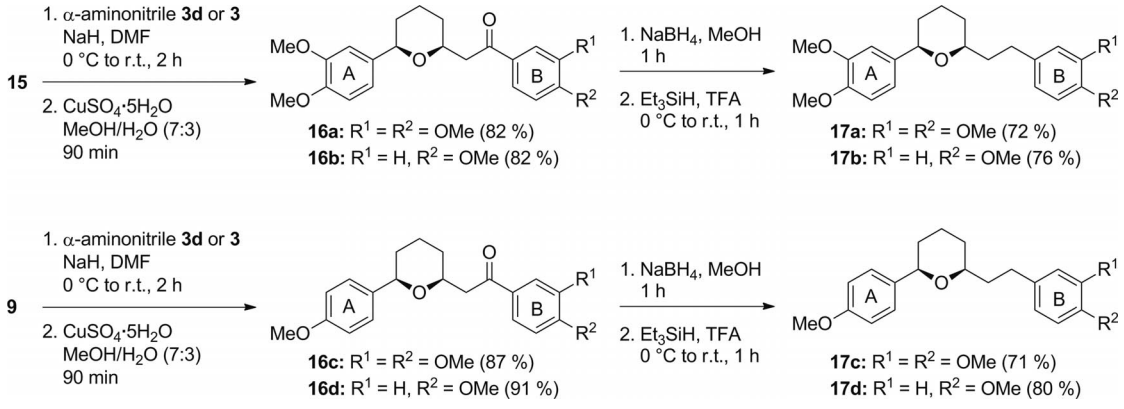
Figure 2. ORTEP diagram of **17c**.

Conclusions

To conclude, the successful synthesis of (+)-centrolobine was achieved through a new disconnection involving the use of acyl anion chemistry. Because the incorporation of the aryl residues in the architecture of (+)-centrolobine occurred at different stages in the developed synthetic scheme, the new strategy disclosed herein is robust and capable of providing ready access to analogues of choice and design.

Experimental Section

General Procedure for the Preparation of Aryl Ketones 6, 6a–d, and 16a–d (Procedure A): To a suspension of NaH (1.2 equiv.) in DMF (8 mL) was added a solution of α-aryl aminonitrile **3**, **3a**–**d** (1.1 equiv.) in DMF (9 mL) at 0 °C under an inert atmosphere. After 20 min, a solution of the bromide (5.7 mmol, 1 equiv.) in DMF (17 mL) was added, and the reaction mixture was stirred for 2 h at



Scheme 5. Synthesis of various analogues of (+)-centrolobine.

room temperature. A saturated solution of NH_4Cl (15 mL) was added, and the mixture was extracted with ethyl acetate (3× 20 mL). The ethyl acetate layer was washed with water (3× 20 mL), dried with Na_2SO_4, and concentrated to obtain alkylated compound **5**. Without further purification, a solution of $CuSO_4·5H_2O$ (5 equiv.) in CH_3OH/H_2O (7:3, 15 mL/g of alkylated compound) was added, and the mixture was heated at reflux at 60 °C for 90 min. The solvents were evaporated under reduced pressure, and water (10 mL) was added to the obtained residue. The aqueous layer was extracted with ethyl acetate (3× 20 mL), and the combined organic layer was washed with a saturated solution of $NaHSO_3$ (3× 15 mL), brine (10 mL), and dried with Na_2SO_4. The solvent was evaporated, and the obtained residue was purified by silica gel column chromatography (ethyl acetate/ hexanes, 2:8) to afford the aryl ketones.

General Procedure for the Stereoselective Cyclization (Procedure B): To a solution of aryl ketone **6** or **6d** (1 equiv.) in methanol (20 mL) was added sodium borohydride (1 equiv.), and the mixture was stirred for 1 h. The solvent was evaporated, and the obtained residue was dissolved in water (10 mL). The aqueous layer was extracted with ethyl acetate (3× 15 mL). The combined organic layer was washed with brine (20 mL), dried with Na_2SO_4, and concentrated. Methanol (40 mL) and *p*TsOH (1 equiv.) were added to the obtained residue, and the mixture was stirred under an inert atmosphere. After complete consumption of the starting material, the solvent was evaporated, and the obtained residue was dissolved in water (15 mL). The aqueous layer was extracted with ethyl acetate (3× 15 mL), and the combined organic layer was washed with brine (20 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexanes, 2:8) to afford *cis*-2,6-disubstituted tetrahydropyrans **8** and **14** from **6** and **6d**, respectively.

General Procedure for the Decarbonylation Reaction: To a solution of aryl ketone **16a**–**d** (1 equiv.) in methanol (5 mL) was added sodium borohydride (1 equiv.), and the mixture was stirred for 1 h. The solvent was evaporated, and the residue was dissolved in water (10 mL). The aqueous layer was extracted with ethyl acetate (3× 15 mL). The combined organic layer was washed with brine (20 mL), dried with Na_2SO_4, and concentrated. The obtained residue was dissolved in CH_2Cl_2 (8 mL) and Et_3SiH (5 equiv.) and CF_3COOH (1 equiv.) were then added at 0 °C under an inert atmosphere. After 15 min, the reaction mixture was warmed to room temperature and then stirred for 45 min. A saturated solution of $NaHCO_3$ (6 mL) was added, and the mixture was extracted with ethyl acetate (3× 10 mL). The ethyl acetate layer was washed with water (3× 20 mL), dried with Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography (ethyl acetate/hexanes, 2:8) to afford the various analogues of (+)-centrolobine in good yields.

Supporting Information (see footnote on the first page of this article): General information, characterization data, copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds, and NOE spectra of compounds **2**, **8**, **14**, and **17a**–**d**.

Acknowledgments

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[11] Crystal data for compound **17c**: Formula: $C_{22}H_{28}O_4$; unit cell parameters: a = 8.3095(6) Å, b = 6.6828(6) Å, c = 17.5760(13) Å, β = 92.693(3)°; space group $P2_1$; CCDC-906158 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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