Functionalized alkoxy arene diazonium salts from paracetamol†

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Arene diazonium tetrafluoroborates can be synthesized from aromatic acetamides *via* a sequence of deacetylation, diazotation and precipitation, induced by anion exchange. The reaction is conducted as a convenient one-flask transformation with consecutive addition of the appropriate reagents. Exchange of solvents or removal of byproducts prior to isolation of the product is not required. The arene diazonium salts are isolated from the reaction mixture by simple filtration. Two complementary protocols are presented, and the utility of the reaction is exemplified for a synthesis of the diarylheptanoid natural product de-*O*-methyl centrolobine.

Introduction

The use of arene diazonium salts in organic synthesis has a long tradition and numerous name reactions are associated with these compounds.[1] Recently, the application of arene diazonium salts as sources for aryl radicals and their use in the functionalization of alkenes has attracted renewed interest.[2–6] Various counterions can be used for these applications, and it was found that the anion may influence the course of the reaction. Another possibility to functionalize alkenes using arene diazonium salts are Pd-catalyzed coupling reactions.[7,8] Although the utility of aromatic diazonium salts for these transformations has been known for more than three decades,[9–28] the number of examples is limited when compared to the analogous aryl iodides or triflates. This is, in light of the beneficial properties commonly reported for these arylating agents, quite surprising: arene diazonium tetrafluoroborates (i) are highly reactive even at ambient temperature, (ii) enable virtually complete suppression of undesired subsequent double bond isomerization and (iii) can be isolated and stored as solids over long periods of time without noticeable decomposition.

A number of methods are available for the synthesis of arene diazonium tetrafluoroborates, and with very few exceptions all of these start from anilines. These methods include the diazotation with $NaNO_2$ and aqueous HBF_4,[29,30] the use of $NOBF_4$[31,32] or organic nitrites in the presence of borontrifluoride etherate[33] or trifluoroacetic acid.[34] A notable exception is a method published by Weiß *et al.*, who used bissilylated anilines in combination with $NOBF_4$ to obtain arene diazonium salts and the corresponding disiloxane.[35]

Over the past few years we[36,37] and others[38–43] reported that arene diazonium tetrafluoroborates are particularly useful for intermolecular Heck-reactions with 2,3-unsaturated heterocycles. With these substrates, the arylation occurs selectively at the 2-position of oxa- and azacycles. We came into this field in the course of target molecule projects directed at the synthesis of *C*-aryl glycosides[44,45] and cyclic and acyclic diarylheptanoids.[46] Examples for the latter class of natural products are centrolobine (**I**), de-*O*-methyl centrolobine (**II**) and centrolobol (**III**), which were all isolated from the heartwood of tropical trees of *Centrolobium sp*.[47,48] (Fig. 1).

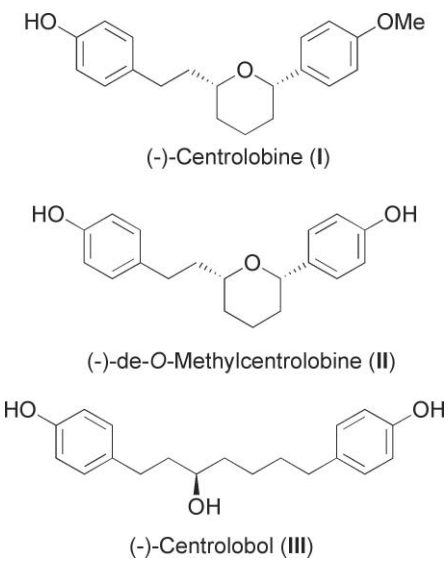

Fig. 1 Diarylheptanoid natural products.

We have recently described a stereodivergent route to all stereoisomers of centrolobine (**I**), in which we introduced the *para*-methoxy phenyl substituent *via* a Heck-reaction with the corresponding diazonium tetrafluoroborate **3a**.[49] **3a** is easily prepared from the only moderately air-sensitive *p*-anisidine by diazotation with $NaNO_2$ and aqueous HBF_4.[29,30] Not surprisingly, all attempts to obtain de-*O*-methyl centrolobine by demethylation of centrolobine resulted in decomposition, due to the harsh conditions which are normally required for the deprotection of methyl ethers.[50] This lead us to the conclusion that other arene diazonium salts with a more easily cleavable alkoxy group are required as coupling reagents, if the target molecule is an unprotected phenol. On the other hand, it is also necessary that the strongly acidic conditions of the diazonium salt formation are tolerated. We thought that a benzyl ether might be a suitable protecting group

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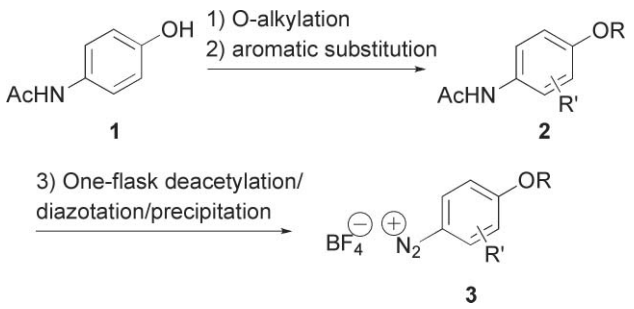
† Electronic supplementary information (ESI) available: Full experimental details and characterization data for all acetanilides **2**; copies of ^1H and ^{13}C NMR spectra for all compounds; copies of IR spectra for all diazonium salts **3**. See DOI: 10.1039/b924619c

and therefore aimed at the synthesis of the *p*-benzyloxy substituted diazonium salt **3b**. This compound has previously been prepared in three steps by benzylation of *p*-nitrophenol, reduction of the nitro group with hydrazine and RANEY®-nickel, and final diazotation with $NaNO_2/HBF_4$.[51] More recently, **3b** was synthesized by diazotation of *para*-benzyloxy aniline (**4b**) with isoamyl nitrite and used as a building block for the synthesis of β-amino acids.[52] The chloride of **3b**, obtained only in solution by diazotation of **4b** with $NaNO_2$, has been used in a Japp–Klingemann reaction for the synthesis of tryptamine derivatives.[53] In light of this literature background, we were unpleasantly surprised to find that **4b** turned out to be much more air-sensitive than *p*-anisidine (**4a**). Thus, with standard laboratory techniques, we were unable to obtain any diazonium salt **3b**, because decomposition of the parent aniline, monitored by ^{1}H-NMR-spectroscopy, is virtually complete on a time scale of minutes. One way to avoid this problem might be to start from substituted acetanilides **2** (Scheme 1), rather than anilines. Acetanilides are normally crystalline and less prone to oxidation than anilines. Very little is known about the reaction of aromatic amides under diazotizing conditions. For instance, an arene diazonium nitrate was obtained when acetanilide was treated with liquid NO_2,[54,55] while exposure to nitrous acid was reported to give the corresponding N-nitroso compound.[56] From a practical point of view, it would be far more promising to deacetylate the acetamide prior to diazotation. For the reasons outlined above, we thought that it would be most convenient to deacetylate the starting acetamides *in situ* and carry out the diazotation and precipitation as a tetrafluoroborate in the same reaction vessel, without removing or exchanging solvents, simply by adding the required reagents in due course.



Scheme 1 General route for the synthesis of arene diazonium compounds from paracetamol.

For the reasons outlined above, we were particularly interested in alkoxy arene diazonium compounds. An ideal starting material, not only for **3b** but also for many other derivatives, should be 4-acetamidophenol (**1**, *INN*: Paracetamol). Following the general synthetic route outlined in Scheme 1, several arene diazonium tetrafluoroborates should become available from paracetamol in just two or three steps *via* *O*-alkylation, aromatic substitution (if required) and one-flask deacetylation/diazotation/precipitation.

Aromatic nitro compounds, which require a reduction prior to the diazotation step,[43] are to some degree an alternative to the acetanilides used in this work. In particular, a substitution pattern at the aromatic core which is better achieved with a nitro substituent, or a very cheap or conveniently available starting material, might be good reasons to consider nitroarenes rather than acetanilides. However, in many cases the route outlined above will have advantages. For instance, acetanilides are more easily substituted than nitro compounds. Nitro group reductions, which often require hydrogen or reducing agents which are incompatible with the subsequent diazotation, are less conveniently performed than deacetylation reactions. Furthermore, acetanilides are less toxic than aromatic nitro compounds.

In this contribution, we report on the synthesis of various diazonium tetrafluoroborates from appropriately functionalized acetanilides, using a deacetylation/diazotation sequence,[57] and the application of this method in the synthesis of the diaryl heptanoid natural product de-*O*-methyl centrolobine (**II**).

Results and discussion

Synthesis of acetanilides 2 from 4-acetamidophenol (1)

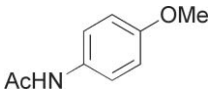
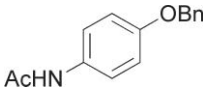
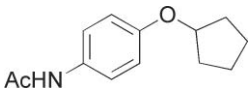
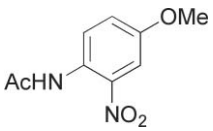
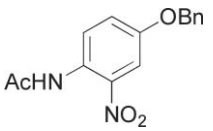
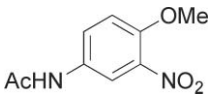
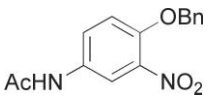
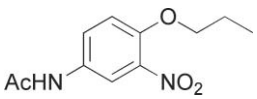
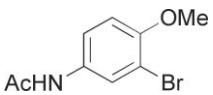
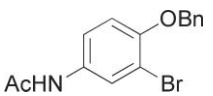
A set of substrates for the one-pot deacetylation-diazotation sequence was synthesized in one or two steps, starting from **1**. Table 1 gives an overview of the substrates used to evaluate the scope of the method, and their synthesis. We will comment briefly on the synthesis of few derivatives. While 2-nitro acetamides **2d**,**e** were obtained in high regioselectivity and good yields using diluted nitric acid, the 3-nitro derivatives were selectively synthesized using a method recently published by Ramana *et al.*[58] Thus, treatment of **2a** with guanidinium nitrate gives **2f** in good yield. Application of this method to **2b** results in partial debenzylation, therefore, **2g** was obtained by nitration of 4-acetamidophenol (**1**), followed by benzylation. These problems were not observed for the propyl derivative **2h**, which was synthesized from **1** in two steps by alkylation and subsequent nitration with guanidinium nitrate, without noticeable formation of the other regioisomer or the dealkylation product. Bromo compounds **2i** and **2j** could only be obtained by bromination of **1**, followed by O-alkylation, because reversal of these steps leads to low yields and poor regioselectivities.

Deacetylation/diazotation sequence: optimization for 3b

We started to investigate the one-flask deacetylation–diazotation–precipitation sequence for **2b**. Hydrolysis of acetanilides in the presence of benzyl ethers has previously been investigated in different context[59] and was found to proceed well if hydrochloric acid and methanol were used at elevated temperatures. In our first experiments, the deacetylation step was investigated in 1 : 1 mixtures of hydrochloric acid and methanol. With 9 M and 6 M aqueous HCl, both acetanilide and benzyl ether were cleaved and only 4-aminophenol could be isolated. By lowering the concentration to 4 M, selective deacetylation could be achieved, and the benzyl ether remains intact. To accomplish the deacetylation-diazotation sequence, **2b** was first treated with a 4 : 1 mixture of 3 M aqueous HCl and methanol at 100 °C for three hours. The mixture was then cooled to 0 °C, and the amine was diazotized *in situ* with aqueous $NaNO_2$, followed by precipitation of the diazonium salt *via* addition of a solid tetrafluoroborate. Following this protocol, a yield of 34% of the desired diazonium tetrafluoroborate **3b** was obtained.

One reason for this rather low yield might be the enhanced solubility of arene diazonium tetrafluoroborates in alcohols. First attempts to optimize the reaction involved variation of the volume

Table 1 Synthesis of acetanilides **2**

No.	Acetanilide	Starting material	Reagents and conditions	Yield
2a[60]		**1**	K_2CO_3, CH_3I, acetone, 65 °C.	Quant.
2b[59]		**1**	K_2CO_3, Benzyl bromide, acetone, 65 °C.	97%
2c		**1**	K_2CO_3, *c*-C_5H_9Br, NaI, acetone, 65 °C.	70%
2d[61]		**2a**	12% HNO_3, 50 °C.	79%
2e[62]		**2b**	12% HNO_3, 50 °C.	94%
2f[58]		**2a**	Guanidinium nitrate, 85% H_2SO_4, 0 °C.	82%
2g		**1**	1) Guanidinium nitrate, 85% H_2SO_4, 0 °C (84%). 2) K_2CO_3, Benzyl bromide, acetone, 65 °C (80%)	67%
2h		**1**	1) K_2CO_3, n-C_3H_7I, acetone, 65 °C (93%). 2) Guanidinium nitrate, 85% H_2SO_4, 0 °C (90%).	84%
2i[63]		**1**	1) Br_2, $AlCl_3$ (10 mol%), 0 °C 20 °C (91%). 2) K_2CO_3, CH_3I, acetone, 65 °C (98%).	89%
2j		**1**	1) Br_2, $AlCl_3$ (10 mol%), 0 °C 20 °C (91%). 2) K_2CO_3, benzyl bromide, acetone, 65 °C (98%).	89%

of alcohol co-solvent and of the alcohol itself under standardized conditions. In 3 M aqueous HCl, without any co-solvent, the sequence failed completely, presumably because the amide is not cleaved in the absence of alcohols. The results are summarized in Table 2: best yields were obtained by using 3 M aqueous HCl and 25 vol % of methanol as a co-solvent. Increasing volumes of co-solvent and the use of ethanol instead of methanol result in lower isolated yields of diazonium salt **3b**. A further improvement was observed by lowering the reaction temperature of the deacetylation step from 100 °C to 90 °C. Under these conditions, **3b** can be obtained as a microcrystalline solid in 65% yield. Apparently, at temperatures above 90 °C debenzylation is becoming a significant problem, and we always observed significantly reduced isolated yields of **3b** or complete failure in these cases. On the other hand, reducing the temperature to 80 °C results in incomplete deacetylation even after eight hours, and the overall yield of **3b** is only 42%. At this point we assumed that a further improvement of the one-pot reaction is only possible if the undesired debenzylation is completely suppressed, and that this might be achieved by using acids with non-nucleophilic counterions. We tested sulfuric acid, but the results were very disappointing. Aqueous HBF_4 in combination with methanol works better, but the yields are still lower than for the optimized conditions in the hydrochloric acid/methanol series (Scheme 2 and Table 2).

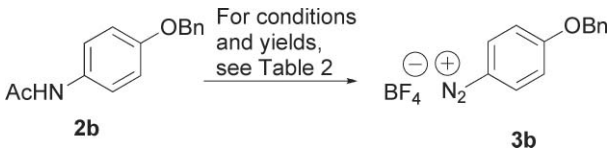
Deacetylation-diazotation sequence in aqueous solution

The optimized conditions discovered for the synthesis of diazonium salt **3b** from acetamide **2b** were next applied to the acetamides **2** listed in Table 1. Although the *para*-methoxy derivative **3a** is

Table 2 Results for the optimization studies

Entry	Co-solvent/amount/mL mmol^{-1}[a]	Acid/c/mol L^{-1}	Yield
1	none	HCl (aq)/3	0%
2	Methanol/0.25	HCl (aq)/3	0%
3	Methanol/0.63	HCl (aq)/3	12%
4	**Methanol/1.25**	**HCl (aq)/3**	**65%**
5	Ethanol/1.25	HCl (aq)/3	37%
6	Methanol/2.50	HCl (aq)/3	61%
7[b]	Methanol/1.25	HCl (aq)/3	42%
8	Ethanol/2.50	H_2SO_4 (aq)/4	18%
9[c]	Methanol/1.25	HBF_4 (aq)/3.6	0%
10[c]	Methanol/1.25	HBF_4 (aq)/2.5	38%
11[c]	Methanol/0.63	HBF_4 (aq)/2.5	45%
12[b,c]	Ethanol/0.63	HBF_4 (aq)/3.6	44%

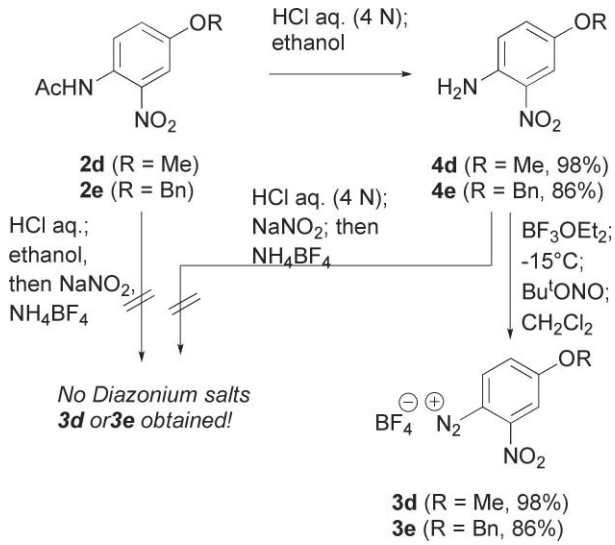
[a] Standardized conditions: **2b**, acid (3.7 mL per mmol of **2b**), co-solvent (x mL per mmol of **2b**) are heated to 90 °C for 3 h; the mixture is cooled to 0 °C, add $NaNO_2$ (1.5 equiv.), stir at 0 °C for 1 h; add NH_4BF_4 (1.5 equiv.). [b] Temperature for deacetylation step was 80 °C. [c] No NH_4BF_4 is added.



Scheme 2 Optimization of deacetylation/diazotation conditions for **3b**.

more conveniently synthesized from 4-methoxyaniline, we also included **2a**, to check if a methyl ether is significantly more stable against dealkylation under acidic conditions. This is indeed the case: even at higher concentrations of hydrochloric acid, and at higher reaction temperatures, the methyl ether remains intact and the diazonium salt **3a** is isolated in 83% yield. The observation that cyclopentyl aryl ethers are common structural elements in pharmaceuticals or drug candidates, such as the estrogen quinestrol[64] or phosphodiesterase inhibitors,[65–67] prompted us to investigate the application of our conditions to acetamide **2c**. *Via* this route, the novel diazonium salt **3c** was obtained. A nitro substituent *ortho* to the acetamide group is obviously a limitation of the method: we were unable to obtain the diazonium salts **3d**,**e** under these conditions. A two step procedure, with isolation of the aniline **4d** (obtained by acidic hydrolysis of the acetanilide **2d**) and subsequent diazotation in aqueous solution under standard conditions, also turned out to be unsuccessful. Remarkably, **3d** has previously been synthesized as its trifluoroacetate from **4d** by Colas and Goeldner using aprotic conditions (trifluoroacetic acid, isoamyl nitrite).[34] We were able to reproduce this result, but discovered that the method developed by Doyle and Bryker (BF_3-etherate, *tert*-butyl nitrite in dichloromethane or ether solvent) also works nicely, giving **3d** as its tetrafluoroborate.[33] Gratifyingly, the two-step procedure also works well for the benzyl-protected derivative **2e**, which is first deacetylated in 86% yield to the aniline **4e**. Diazotation of **4e** under the same conditions used for **4d** works well, while diazotation with $NaNO_2$ in aqueous acidic medium fails completely. The benzyl protected diazonium salt **3e** has very recently been used in a synthesis of the antipsychotic Aripiprazole, however, without giving details concerning its synthesis (Scheme 3).[68]

In contrast to the 2-nitro diazonium salts **3d**,**e**, the 3-nitro-regioisomers **3f–h** can be synthesized from acetamides **2f–h** *via* the



Scheme 3 Two-step deacetylation-diazotation for *ortho*-nitro acetanilides.

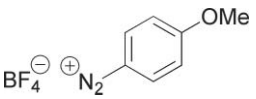
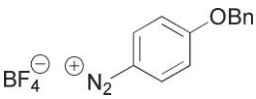
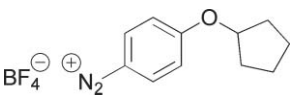
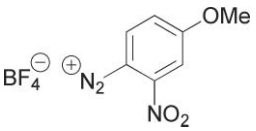
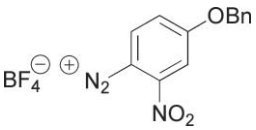
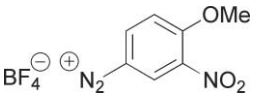
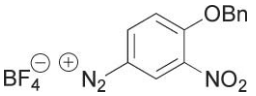
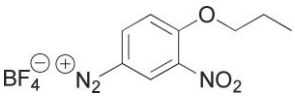
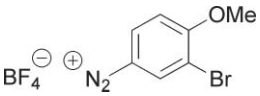
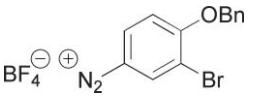
one-pot deacetylation-diazotation sequence. 3-Bromoacetanilides **2i**,**j** are also converted to the corresponding diazonium salts **3i**,**j** using this sequence. Surprisingly, for both substitution patterns significantly lower yields are observed for the 4-methoxy derivatives. A possible explanation might be a rather high solubility of the salts **3f** and **3i** in water, while the corresponding benzyl or propyl derivatives are much less hydrophilic (Table 3).

Deacetylation-diazotation sequence in anhydrous medium

Inspired by the remarkable results obtained for the diazotation of anilines **4d** and **4e** using Doyle's method, we investigated a one-flask deacetylation-diazotation sequence under organic anhydrous conditions (Table 3).

The deprotection of acetamides in the presence of a Lewis- rather than a Brønsted-acid was described by Sihlbom, who used borontrifluoride in methanol for the deacylation of various amides.[69] Obviously, a nucleophilic, protic solvent is necessary to achieve an efficient cleavage of amides, and the question remained if Doyle's diazotation method is compatible with protic solvents. As a test reaction, acetanilide **2a** was treated with the commercially available borontrifluoride methanol adduct in dry methanol under reflux to achieve a cleavage of the acetanilide. After cooling the mixture to −15 °C and addition of *tert*-butyl nitrite, the desired arene diazonium salt **3a** was isolated in 72% yield. Next, these conditions were applied to the other acetanilides **2b–j**. In nearly all cases the yields were significantly better or at least similar compared to the yields obtained in water/alcohol mixtures in the presence of hydrochloric acid. A notable exception is **2c**: For this derivative the sequence fails completely in organic medium, which can probably be attributed to a cleavage of the cyclopentyl ether. The most remarkable results were found for diazonium salts **3d** and **3e**: under the "organic" conditions described above, yields of 92% and 82%, respectively, were obtained, while under aqueous-Brønsted-acidic conditions the diazonium salt formation fails completely. The results obtained for the synthesis of diazonium salts **3a–j** from the corresponding acetanilides *via* the one-pot deacetylation-diazotation sequence under

Table 3 Deacetylation/diazotation sequence in aqueous [a] and anhydrous [b] media

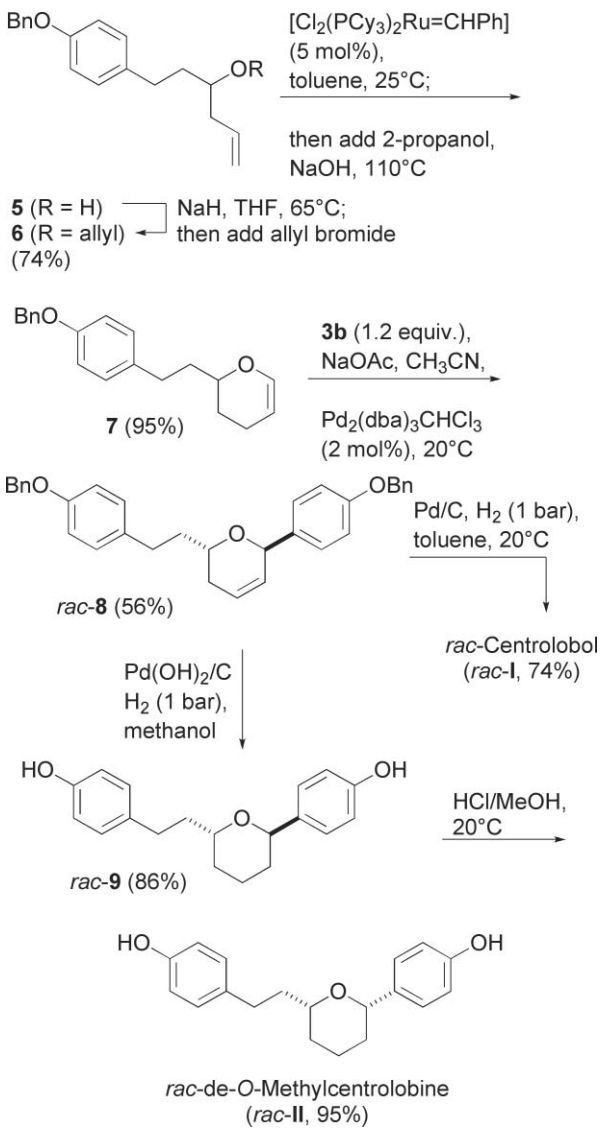
2	Diazonium salt	3	Yield[a]	Yield[b]
2a		**3a**	83%	72%
2b		**3b**	65%	71%
2c		**3c**	42%	0%
2d		**3d**	0%	92%
2e		**3e**	0%	82%
2f		**3f**	32%	72%
2g		**3g**	58%	83%
2h		**3h**	68%	66%
2i		**3i**	25%	39%
2j		**3j**	52%	66%

[a] *Reagents and conditions*: HCl (aq), ethanol, reflux; then 0 °C, $NaNO_2$; NH_4BF_4, 0 °C. [b] *Reagents and conditions*: BF_3·MeOH, dry methanol, 65 °C, then −15 °C, Bu^{t}ONO, −15 °C→0 °C.

aqueous-Brønsted-acidic or organic-Lewis-acidic conditions are summarized and compared in Table 3.

Synthesis of *rac*-de-*O*-methyl centrolobine

While several syntheses of centrolobine[70] (Fig. 1) have been published, we are aware of only one synthesis of the closely related de-*O*-methyl centrolobine (**II**).[71] We used a protected arene diazonium salt obtained *via* the methods described herein for the synthesis of this cyclic diaryl heptanoid. Starting from known homoallylic alcohol **5**,[72] the allyl ether **6** was synthesized and subsequently subjected to the conditions of a Tandem RCM-isomerization sequence.[73–75] This resulted in the required dihydropyran **7** in excellent yield, which was then reacted with diazonium salt **3b** in the presence of 2 mol% of $Pd_2(dba)_3$·$CHCl_3$ catalyst. The product of this Heck reaction, dihydropyran **8**, was obtained as a single diastereoisomer. Attempts to achieve simultaneously a debenzylation and hydrogenation of the C–C-double bond resulted initially in a quantitative conversion of **8** to *rac*-centrolobol (**I**, Fig. 1), when Pd/C was used as a catalyst. A similar ring opening has previously been observed by Chandrasekhar *et al.*[76] and by Jennings and Clemens[77] in the course of their centrolobine syntheses. Both groups obtained the same mono-*O*-methyl centrolobol derivative. We found, after some experimentation, that clean hydrogenation and debenzylation could be achieved with $Pd(OH)_2$/C as a catalyst and 1 bar of hydrogen. Under these conditions the *trans*-configured epimer of de-*O*-methyl centrolobine (**9**) was obtained, which underwent quantitative isomerization to the *cis*-diastereomer, de-*O*-methyl centrolobine (**II**) in the presence of an acid (Scheme 4).



Scheme 4 Synthesis of *rac*-de-*O*-methyl centrolobine (*rac*-**II**).

Conclusions

We have developed two efficient one-flask procedures for the synthesis of aromatic diazonium salts from acetanilides. We were particularly interested in the synthesis of diazonium salts bearing additional ether functionalities, including easily removable benzyl ethers. For these compounds, the cheap and commercially available 4-acetamidophenol (*INN*: Paracetamol) was identified as the ideal starting material. The protocols described in this work rely on a deacetylation *in situ*, using either an aqueous or an anhydrous organic medium, and a subsequent diazotation. Notably, it is not necessary to isolate the aniline intermediate, which can be a significant advantage in those cases where the aromatic amine is highly air-sensitive. Further advantages of this route are i) the opportunity to selectively alkylate an OH-group without competing alkylation of the amino group, ii) the possibility to functionalize the aromatic moiety using transformations that would not work well (or with different selectivities) for anilines. The synthesis of de-*O*-methyl centrolobine uses a Heck arylation of a cyclic enol ether with *para*-benzyloxybenzene diazonium tetrafluoroborate (**3b**) as a key step. Further applications of our route to aromatic diazonium tetrafluoroborates and their application in the synthesis of interesting target molecules are currently investigated.

Experimental

General procedures for deacetylation/diazotation reactions

Reaction in aqueous medium. A suspension of the corresponding acetanilide **2** (4.2 mmol) in hydrochloric acid (3M, 15 mL) and methanol (5 mL) was heated to reflux until the solid was completely dissolved (approximately 5 h). The resulting clear solution was cooled to 0 °C, and solid $NaNO_2$ (0.44 g, 6.3 mmol) was added in small portions. Stirring at this temperature was continued for 1 h, and NH_4BF_4 (0.66 g, 6.3 mmol) was then added in small portions. The corresponding diazonium tetrafluoroborate started to precipitate after a few minutes, and stirring at 0 °C was further continued for 30 min to ensure complete precipitation. The ice-cold suspension was filtered *via* a Büchner-funnel, and the solid was subsequently washed with cold water (10 mL), ethanol (10 mL), and diethyl ether (50 mL). It was dried in a stream of air to yield the corresponding diazonium tetrafluoroborates **3** as colourless solids.

Reaction in anhydrous medium. To a solution of the corresponding acetanilide **2** (3.0 mmol) in dry methanol (5 mL) was added boron trifluoride-methanol (9.1 mmol, 1.20 g, 0.98 mL). The solution was heated to reflux under an atmosphere of dry nitrogen until the starting acetanilide was completely consumed, as indicated by TLC. The mixture was then cooled to −15 °C and *tert*-butyl nitrite (4.5 mmol, 0.47 g, 0.54 mL) was added. Over a period of 15 min a colourless precipitate was formed. Stirring was continued for another hour, and the solid was collected by filtration, washed subsequently with cold ethanol (20 mL) and MTBE (20 mL) to give the corresponding diazonium salt **3**.

Arene diazonium salts 3

***para*-Methoxybenzenediazonium tetrafluoroborate (3a).** In aqueous medium: obtained from **2a** (3.00 g, 18.0 mmol). Yield: 83% (3.30 g, 14.9 mmol). In anhydrous medium: obtained from **2a** (500 mg, 3.0 mmol). Yield: 72% (480 mg, 2.2 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.61 (d, 2H, J = 9.4 Hz), 7.48 (d, 2H, J = 9.4 Hz), 4.04 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, APT) δ 168.8, 136.1, 117.3, 103.3, 57.4; IR (KBr-disc) ν/cm^{-1} 3120 (w), 2251 (m, N_2), 1583 (s), 1569 (s), 1494 (s), 1290 (s), 1036 (s); MS (ESI) m/z 135 (100%, $(M)^+$), 107 (51%), 92 (60%); HRMS (ESI) calc. for $C_7H_7N_2O^+$ $(M)^+$ 135.0553. Found 135.0535.

***para*-Benzyloxybenzenediazonium tetrafluoroborate (3b).** In aqueous medium: obtained from **2b** (1.00 g, 4.1 mmol). Yield: 65% (0.81 g, 2.7 mmol). In anhydrous medium: obtained from **2b** (731 mg, 3.0 mmol). Yield: 71% (690 mg, 2.2 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, 2H, J = 9.4 Hz), 7.56 (d, 2H, J = 9.4 Hz), 7.51–7.39 (5H), 5.42 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.8, 136.2, 134.9, 128.7, 128.7, 128.4, 117.9, 103.7, 71.4; IR (KBr-disc) ν/cm^{-1} 3112 (m), 2253 (s, N_2), 1580 (s), 1488 (s), 1280 (s), 1097 (s); MS (FAB+LR) m/z 212 (95%, $[M]^+$), 184 (30%); HRMS (FAB) calc. for $C_{13}H_{11}N_2O^+$ $(M)^+$ 211.0866. Found 211.0888; Anal. calc. for $C_{13}H_{11}BF_4N_2O$: C, 52.4%; H, 3.7%; N, 9.4%. Found: C, 52.7%; H, 3.6%; N, 9.6%.

***para*-Cyclopentyloxyphenyl diazonium tetrafluoroborate (3c).** In aqueous medium: obtained from **2c** (1.80 g, 8.2 mmol). Yield: 42% (1.00 g, 3.6 mmol). In anhydrous medium: **3c** is not accessible using this protocol. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.72 (d, J = 9.3, 2H), 7.49 (d, J = 9.3, 2H), 5.15 (m, 1H), 2.13–1.94 (2H), 1.79–1.62 (6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 131.6, 118.2, 102.6, 82.2, 32.2, 23.6; IR (KBr-disc) ν/cm^{-1} 2959 (w), 2271 (m, N_2), 1583 (s), 1481 (m) 1337 (m), 1279 (s), 1063 (s), 1028 (s); MS (ESI) m/z 189 (100%, M^+), 190 (20%); HRMS (ESI) calc. for $C_{11}H_{13}N_2O^+$ $(M)^+$ 189.1022. Found: 189.1028.

4-Methoxy-2-nitrobenzenediazonium tetrafluoroborate (3d). In aqueous medium: **3d** is not accessible using this protocol. In anhydrous medium: obtained from **2d** (636 mg, 3.0 mmol). Yield: 92% (742 mg, 2.8 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (d, J = 9.3, 1H), 8.27 (d, J = 2.5, 1H), 7.89 (dd, J = 2.6, 9.3, 1H), 4.19 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 169.4, 147.6, 139.2, 120.3, 115.8, 98.7, 58.9; IR (KBr-disc) ν/cm^{-1} 3412 (m), 2249 (s, N_2), 1601 (s), 1561 (s), 1348 (s); MS (ESI) m/z 180 (100%), 123 (57%), 91 (57%); HRMS (ESI) calc. for $C_7H_6N_3O_3^+$ $(M)^+$ 180.0409. Found 180.0427.

4-Benzyloxy-2-nitrobenzenediazonium tetrafluoroborate (3e). In aqueous medium: **3e** is not accessible using this protocol. In anhydrous medium: obtained from **2d** (867 mg, 3.0 mmol). Yield: 82% (850 mg, 2.5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (d, J = 9.2, 1H), 8.38 (d, J = 2.5, 1H), 7.97 (dd, J = 2.5, 9.3, 1H), 7.58–7.36 (5H), 5.59 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.4, 147.6, 139.1, 134.3, 128.8, 128.7, 128.5, 120.7, 116.4, 98.9, 72.9; IR (KBr-disc) ν/cm^{-1} 3438 (m), 2242 (s, N_2), 1596 (s), 1552 (s), 1309 (s); MS (ESI) m/z 256 (56%), 241 (18%), 91 (100%). HRMS (ESI) calc. for $C_{13}H_{10}N_3O_3^+$ $(M)^+$ 256.0722. Found 256.0701.

4-Methoxy-3-nitrobenzenediazonium tetrafluoroborate (3f). In aqueous medium: obtained from **2f** (1.00 g, 4.8 mmol). Yield: 32% (0.40 g, 1.5 mmol). In anhydrous medium: obtained from **2f** (637 mg, 3.0 mmol). Yield: 72% (590 mg, 2.2 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.40 (d, J = 2.6, 1H), 8.87 (dd, J = 2.6,

9.6, 1H), 7.91 (d, $J = 9.6$, 1H), 4.22 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 161.3, 139.0, 138.3, 131.6, 117.8, 104.8, 59.3; IR (KBr disc) ν/cm^{-1} 3132 (m), 2275 (s, N_2), 1599 (s), 1540 (s), 1300 (s); MS (ESI) m/z 180 (100%), 152 (12%); HRMS (ESI) calc. for $C_7H_6N_3O_3^+$ $(M)^+$ 180.0409. Found 180.0416.

4-Benzyloxy-3-nitrophenyldiazonium tetrafluoroborate (3g). In aqueous medium: obtained from **2g** (0.30 g, 1.1 mmol). Yield: 58% (0.21 g, 0.6 mmol). In anhydrous medium: obtained from **2g** (867 mg, 3.0 mmol). Yield: 83% (862 mg, 2.5 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.43 (d, $J = 2.5$, 1H), 8.89 (dd, $J = 2.5$, 9.5, 1H), 8.01 (d, $J = 9.5$, 1H), 7.55–7.29 (m, 5H), 5.62 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.2, 138.9, 138.5, 134.1, 131.7, 128.8, 128.7, 127.9, 118.5, 105.1, 73.1; IR (KBr-disc) ν/cm^{-1} 3425 (m), 2271 (s, N_2), 1594 (s), 1563 (s), 1299 (s); MS (ESI) m/z 256 (100%), 239 (11%), 182 (16%), 91 (71%); HRMS (ESI) calc. for $C_{13}H_{10}N_3O_3^+$ $(M)^+$ 256.0722. Found 256.0742.

3-Nitro-4-propoxybenzenediazonium tetrafluoroborate (3h). In aqueous medium: obtained from **2h** (0.50 g, 2.1 mmol). Yield: 68% (0.42 g, 1.8 mmol). In anhydrous medium: obtained from **2h** (722 mg, 3.0 mmol). Yield: 66% (590 mg, 2.0 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.39 (d, $J = 2.6$, 1H), 8.85 (dd, $J = 2.6$, 9.5, 1H), 7.90 (d, $J = 9.6$, 1H), 4.44 (t, $J = 6.3$, 2H), 1.82 (tq, $J = 6.3$, 7.4, 2H), 1.00 (t, $J = 7.4$, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.7, 139.0, 138.4, 131.7, 118.2, 104.5, 73.6, 21.4, 10.0; IR (KBr-disc) ν/cm^{-1} 3125 (m), 2974 (m), 2281 (s, N_2), 1596 (s), 1355 (s); MS (ESI) m/z 208 (100%), 180 (28%), 138 (51%), 91 (16%); HRMS (ESI) calc. for $C_9H_{10}N_3O_3^+$ $(M)^+$ 208.0722. Found 208.0718.

3-Bromo-4-methoxybenzenediazonium tetrafluoroborate (3i). In aqueous medium: obtained from **2i** (0.50 g, 2.1 mmol). Yield: 25% (0.15 g, 0.5 mmol). In anhydrous medium: obtained from **2i** (739 mg, 3.0 mmol). Yield: 39% (590 mg, 1.2 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (d, $J = 2.5$, 1H), 8.72 (dd, $J = 2.5$, 9.3, 1H), 7.65 (d, $J = 9.3$, 1H), 4.15 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.3, 136.6, 136.1, 114.7, 111.7, 104.8, 58.7; IR (KBr-disc) ν/cm^{-1} 3439 (m), 2241 (s, N_2), 1562 (s), 1485 (s), 1297 (s); MS (ESI) m/z 185 (100%), 170 (6%), 155 (17%), 91 (2%); HRMS (ESI) calc. for $C_7H_6BrN_2O^+$ $(M)^+$ 212.9664. Found 212.9678.

4-Benzyloxy-3-bromobenzenediazonium tetrafluoroborat (3j). In aqueous medium: obtained from **2j** (0.40 g, 1.3 mmol). Yield: 52% (0.25 g, 0.7 mmol). In anhydrous medium: obtained from **2j** (969 mg, 3.0 mmol). Yield: 66% (750 mg, 2.0 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.99 (d, $J = 2.5$, 1H), 8.72 (dd, $J = 2.5$, 9.4, 1H), 7.75 (d, $J = 9.4$, 1H), 7.57–7.34 (5H), 5.53 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.3, 136.79, 135.9, 134.6, 128.7, 128.7, 127.9, 115.58, 112.2, 105.1, 72.4; IR (KBr-disc) ν/cm^{-1} 3454 (m), 2972 (m), 2243 (s, N_2), 1563 (s), 1296 (s); MS (ESI) m/z 289 (19%), 261 (24%), 185 (6%), 91 (100%); HRMS (ESI) calc. for $C_{13}H_{10}BrN_2O^+$ $(M)^+$ 288.9976. Found 288.9991.

Synthesis of de-*O*-methyl centrolobine

1-(3-(Allyloxy)hex-5-enyl)-4-(benzyloxy)benzene (6). To a solution of alcohol **5** (1.91 g, 6.8 mmol) in dry and degassed THF (30 mL) was added NaH (60% dispersion in mineral oil, 300 mg, 7.5 mmol). The mixture was heated to reflux for 30 min., cooled to ambient temperature, and allyl bromide (0.71 mL, 8.2 mmol) was added dropwise. The mixture was again heated to reflux for one hour, then cooled to ambient temperature and quenched by addition of water (25 mL). It was extracted with diethyl ether (100 mL), and the organic layer was separated, dried with $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography on silica to give the title compound **6** as a colourless liquid (1.63 g, 5.0 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.31 (5H), 7.11 (d, $J = 8.5$, 2H), 6.91 (d, $J = 8.6$, 2H), 5.95 (dddd, $J = 5.6$, 5.6, 10.4, 17.2 1H), 5.82 (dddd, $J = 7.1$, 7.2, 10.2, 17.2 1H), 5.29 (ddm, $J = 1.6$, 17.2, 1H), 5.17 (ddm, $J = 1.3$, 10.3, 1H), 5.11–5.06 (2H), 5.05 (s, 2H), 4.07 (dd, $J = 5.6$, 12.6, 1H), 3.96 (dd, $J = 5.6$, 12.6, 1H), 3.39 (m, 1H), 2.66 (ddd, $J = 5.9$, 9.3, 13.6, 1H), 2.59 (ddd, $J = 5.9$, 9.3, 13.6, 1H), 2.40–2.27 (2H), 1.86–1.73 (2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 136.9, 134.9, 134.4, 134.3, 129.0, 128.2, 127.5, 127.1, 116.7, 116.3, 114.4, 77.4, 69.7, 69.7, 38.0, 35.5, 30.4; IR (NaCl-film) ν/cm^{-1} 2930 (w), 2860 (w), 1610 (w), 1510 (s), 1454 (w), 1240 (s), 1078 (m); LRMS (FAB) m/z 322 (13%) $(M + H)^+$, 257 (16%); HRMS (FAB) calc. for $C_{22}H_{26}O_2^+$ $(M + H)^+$ 322.1933. Found 322.1964; Anal. calc. for $C_{22}H_{26}O_2$: C, 81.9%; H, 8.1%. Found C, 81.4%; H, 9.0%.

2-(4-(Benzyloxy)phenethyl)-3,4-dihydro-2*H*-pyran (7). To a solution of **6** (0.99 g, 3.1 mmol) in dry and degassed toluene (25 mL) was added $[Cl_2(PCy_3)_2RuCHPh)]$ (125 mg, 5 mol%) under an atmosphere of dry argon. The solution was heated to 90 °C for two hours, resulting in complete conversion of the starting material. 2-Propanol (3 mL) and solid NaOH (32 mg, 0.8 mmol) were added, and heating to reflux was continued for two hours. TLC revealed complete consumption of the intermediate metathesis product and formation of the cyclic enol ether. All volatiles were evaporated, and the residue was purified by flash chromatography on silica (eluent cyclohexane/MTBE 10 : 1) to give the title compound **7** (0.87 g, 2.9 mmol, 95%). This material is sufficiently pure for further transformations. If required, further purification is possible by recrystalization from cyclohexane, mp 38 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.37 (5H), 7.13 (d, $J = 8.6$, 2H), 6.91 (d, $J = 8.6$, 2H), 6.40 (d, $J = 6.1$, 1H), 5.05 (s, 2H), 4.67 (ddd, $J = 2.4$, 4.8, 6.1, 1H), 3.79 (m, 1H), 2.75 (dddd, $J = 5.5$, 5.5, 9.8, 9.8, 1H), 2.66 (dddd, $J = 6.9$, 9.5, 10.4, 13.9 1H), 2.06 (m, 1H), 1.99–1.89 (2H), 1.85 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 143.7, 137.2, 134.4, 129.4, 128.5, 127.9, 127.4, 114.7, 100.4, 74.1, 70.1, 37.2, 30.6, 27.9, 19.8; IR (KBr-disc) ν/cm^{-1} 3052 (m), 3029 (m), 2928 (m), 2847 (w), 1649 (s), 1610 (m), 1581 (w), 1512 (s), 1453(s), 1383 (m), 1297 (w), 1176 (w), 1053 (m), 1023 (m); LRMS (FAB) m/z 294 ($(M)^+$, 14%), 197 (12%), 91 (100%); HRMS (FAB) calc. for $C_{20}H_{22}O_2$ $(M)^+$ 294.1620. Found 294.1631; Anal. calcd. for $C_{20}H_{22}O_2$: C, 81.6%; H, 7.5%. Found C, 81.0%; H, 7.7%.

(2*SR*,6*RS*)-2-(4-(Benzyloxy)phenethyl)-6-(4-(benzyloxy-phenyl)-3,6-dihydro-2*H*-pyran (*rac*-8). To a solution of enol ether **7** (422 mg, 1.4 mmol) and diazonium salt **3b** (512 mg, 1.7 mmol) in acetonitrile (10 mL) was added NaOAc (469 mg, 5.7 mmol), followed by $Pd_2(dba)_3{\cdot}CHCl_3$ (30 mg, 2 mol%). Immediately after the Pd-catalyst was added, an evolution of gas was observed, which ceased after approximately 3 h. The mixture was concentrated, and all inorganics were removed by filtration of the mixture over a short pad of silica. The silica pad was thoroughly washed with MTBE, and all volatiles were removed *in vacuo*. The residue was purified

by recrystallization from cyclohexane-diethyl ether, to give the title compound *rac*-**8** (0.37 g, 0.8 mmol, 56%) as colourless crystals, mp 99 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, J = 7.3, 2H), 7.41–7.30 (10H), 6.98 (d, J = 8.6, 2H), 6.81 (d, J = 8.6, 1H), 6.76 (d, J = 8.6, 1H), 6.03 (ddm, J = 5.0, 10.2, 1H), 5.96 (dm, J = 10.2, 1H), 5.25 (s(br), 1H), 5.09 (s, 2H), 4.99 (s, 2H), 3.49 (m, 1H), 2.64 (ddd, J = 4.7, 8.6, 13.7, 1H), 2.44 (ddd, J = 8.2, 8.2, 13.8, 1H), 2.07 (ddm, J = 9.6, 17.5, 1H), 1.97 (ddd, J = 4.0, 4.0, 17.6, 1H), 1.82 (dddd, J = 5.0, 8.7, 8.7, 13.8, 1H), 1.62 (dddd, J = 3.6, 8.7, 8.7, 13.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 156.8, 137.2, 137.0, 134.5, 133.6, 129.8, 129.4, 128.6, 128.5, 128.0, 127.8, 127.6, 127.5, 127.4, 125.9, 114.5, 114.5, 73.8, 70.1, 70.0, 65.8, 37.6, 31.2, 30.6; IR (KBr-disc) ν/cm^{-1} 3433 (w), 3033 (w), 2910 (w), 2887 (m), 2856 (w), 1610 (m), 1582 (w), 1510 (s), 1454 (m), 1383 (m), 1297 (w), 1238 (s), 1174 (s), 1112 (w), 1081 (m), 1066 (m), 1045 (m); LRMS (FAB) m/z 476 ([M +H]$^+$, 13%), 197 (11%), 136 (65%), 91 (55%); HRMS (FAB) calc. for $C_{33}H_{32}O_3$ (M)$^+$ 476.2351. Found 476.2381; Anal. calcd. for $C_{33}H_{32}O_3$: C, 83.2%; H, 6.8%. Found C, 83.0%; H, 6.6%.

***rac-epi*-De-*O*-methyl centrolobine (*rac*-9).** To a solution of *rac*-**8** (150 mg, 0.32 mmol) in methanol (20 mL) was added $Pd(OH)_2/C$ (20 wt% Pd based on dry mass, 9 mg). The suspension was saturated with hydrogen and kept under an atmosphere of hydrogen (1 bar) for 12 h. The solvent was evaporated, and the residue was purified by flash chromatography on silica (hexanes-ethyl acetate 1 : 1) to give the title compound *rac*-**9** (81 mg, 0.28 mmol, 86%) yield as a colourless solid, mp 186 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.20 (d, J = 8.5, 2H), 6.99 (d, J = 8.5, 2H), 6.76 (d, J = 8.6, 2H), 6.68 (d, J = 8.5, 2H), 4.73 (dd, J = 4.1, 6.6, 1H), 3.73 (ddd, J = 4.9, 8.9, 13.8, 1H), 2.65 (ddd, J = 5.5, 9.9, 14.2, 1H), 2.50 (ddd, J = 6.8, 9.5, 13.8, 1H), 2.06 (dddd, J = 5.4, 9.3, 9.7, 14.4, 1H), 1.97–1.57 (6H), 1.45 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 157.8, 156.4, 134.5, 134.3, 130.4, 129.2, 116.2, 116.2, 73.6, 73.0, 36.2, 32.4, 31.6, 31.0, 20.2; IR (KBr-disc) ν/cm^{-1} 3325 (m), 2933 (m), 2856 (m), 1613 (m), 1512 (s), 1452 (m), 1240 (s), 1071 (m), 1024 (m); LRMS (ESI) m/z 227 (100%), 299 (42%); HRMS (ESI) calc. for $C_{19}H_{23}O_3^+$ (M+H)$^+$: 299.1647. Found 299.1658; Anal. calcd. for $C_{19}H_{22}O_3$: C, 76.5%; H, 7.4%. Found C, 75.9%, H, 7.4%.

***rac*-De-*O*-methylcentrolobine (*rac*-II).** To a solution of *rac*-**9** (40 mg, 0.13 mmol) in methanol (1.3 mL) was added HCl (aq., 4 M, 67 µL, 0.26 mmol). The solution was stirred for 12 h at ambient temperature and then diluted with MTBE (10 mL). The organic layer was separated, washed with water, and the aqueous layer was extracted with MTBE. The combined organic extracts were dried with $MgSO_4$, filtered, and all volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica (hexanes–MTBE 1 : 1) to give *rac*-de-*O*-methyl centrolobine (**II**) (38 mg, 0.12 mmol, 95%), mp 162 °C. ^{1}H NMR (300 MHz, CD_3OD) δ 7.19 (d, J = 8.4, 2H), 6.99 (d, J = 8.5, 2H), 6.76 (d, J = 8.6, 2H), 6.68 (d, J = 8.5, 2H), 4.23 (dd, J = 1.8, 10.9, 1H), 3.43 (m, 1H), 2.70–2.51 (2H), 1.94–1.46 (8H), 1.27 (1H); ^{13}C-NMR (75 MHz, CD_3OD) δ 157.8, 156.4, 135.8, 134.6, 130.5, 128.7, 116.2, 116.0, 81.2, 79.0, 39.8, 34.4, 32.6, 31.9, 25.2; IR (KBr-disc) ν/cm^{-1} 3324 (m), 2935 (m), 2858 (m), 2360 (w), 1614 (m), 1514 (s), 1445 (m), 1228 (s), 1072 (m), 1025 (m); LRMS (ESI) m/z 187 (50%), 281 (40%), 299 (100%); HRMS (ESI) calc. for $C_{19}H_{23}O_3^+$ (M+H)$^+$ 299.1647. Found 299.1629; Anal. calcd. for $C_{19}H_{22}O_3$: C, 76.5%; H, 7.4%. Found C, 75.9%; H 7.4%.

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