Natural Product Synthesis

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A Synthetic Study of Atropurpuran: Construction of a Pentacyclic Framework by an Intramolecular Reverse-Electron-Demand Diels–Alder Reaction**

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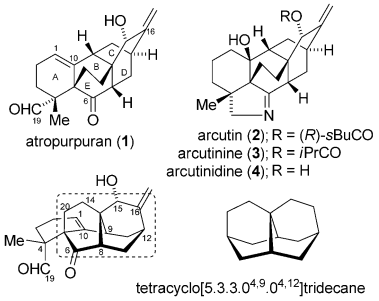
Aconitum is a genus of flowering plants that produce a variety of poisons and compounds of medicinal importance. The fascinating bioactivities of these compounds arise from C_{19} and C_{20} diterpene alkaloids, such as aconitine, hetisine, atisine, and kobusine.[1] Isolation of non-alkaloidal diterpenes from the genus *Aconitum*, however, has rarely been reported.[2] In 2009, Wang and co-workers reported the isolation of the structurally unique non-alkaloidal diterpene atropurpuran (**1**)[3] from *Aconitum hemsleyanum* var. *atropurpureum* (Scheme 1). The structure of atropurpuran features an

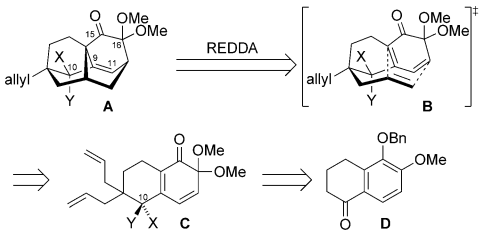


Scheme 1. Structure of atropurpuran and related compounds.

unprecedented cage-like skeleton that consists of five six-membered rings (A, B, C, D, and E rings). Intriguingly, the B, C, D, and E rings constitute the tetracyclo[5.3.3.3.0^{4,9}.0^{4,12}]-tridecane skeleton, which includes two bicyclo[2.2.2]octane units. This unusual cage-like structural motif is only found in a few members of the diterpene alkaloids, namely arcutin (**2**), arcutinine (**3**), and arcutinidine (**4**), which were isolated from the roots of *Aconitum arcuatum*.[4] Compounds **2**–**4** are closely related to atropurpuran and only differ in the substitution at C-19 (i.e., by forming a 1-pyrroline ring) and the hydroxylation of the C-1,10 double bond.

Despite the intriguing biosynthetic and structural properties of the tetracyclo[5.3.3.3.0^{4,9}.0^{4,12}]tridecane skeleton, there are no previous reports that describe efforts to synthesize this compound. Consequently, at the outset of our synthetic investigation on **1**, we attempted to establish a methodology for the construction of the tetracyclic skeleton. Herein, we report the first entry to a tetracyclo[5.3.3.3.0^{4,9}.0^{4,12}]tridecane skeleton and the pentacyclic carbon framework of **1** through an intramolecular Diels–Alder reaction of masked *ortho*-benzoquinone (MOB).

Our strategy towards the synthesis of the tetracyclic skeleton **A** was to utilize a reverse-electron-demand Diels–Alder (REDDA) reaction of MOB (Scheme 2). The REDDA reaction with MOB has recently emerged as a powerful tool



Scheme 2. Synthetic strategy toward the tetracyclic framework.

for the construction of highly functionalized complex molecules.[5,6] We envisaged that the intramolecular REDDA reaction of MOB **C** would directly provide the requisite tetracyclic framework **A** via a transition state **B** to give an anti-Bredt compound. The ketoacetal group at C-15,16[7] in **A** could serve as a potential precursor for introducing requisite functional groups in **1**. Based on steric and electronic considerations, the intramolecular REDDA reaction seems to be highly dependent on the substituent at C-10 (X and Y). Although the sp^2-hybridized C-10 is suitable for the synthesis of **1**, we reasoned that the cycloadduct might be relatively unstable because of a bridgehead double bond at C-9,11 with a conjugated sp^2-hybridized carbon center. Therefore, we decided to prepare several keto- and alkoxy-substituted precursors and investigate the feasibility of the REDDA reaction of these precursors. MOB **C** is easily prepared from tetralone **D** by diallylation and oxidative dearomatization with hypervalent iodine.

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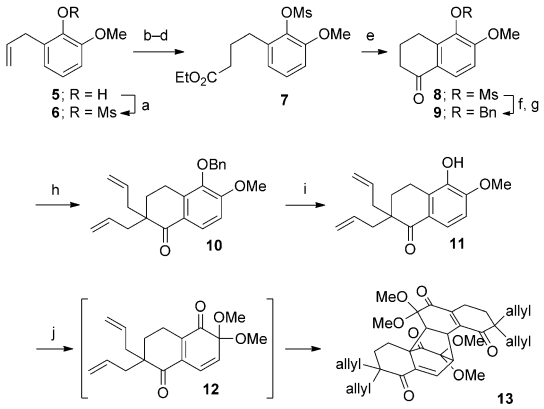
The preparation of the REDDA precursor commenced with the protection of *ortho*-eugenol **5** with a mesyl group (Scheme 3). According to the reported procedure for 5,6-

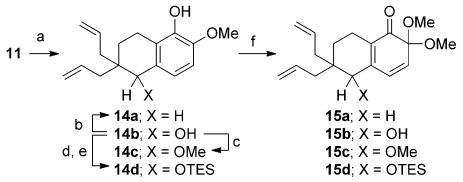


Scheme 3. Attempts to prepare keto-substituted MOB. a) MsCl, TEA, CH_2Cl_2, 0 °C, 93 %; b) O_3, CH_2Cl_2, −78 °C, then Me_2S, 0 °C, 72 %; c) triethyl phosphonoacetate, NaH, THF, 0 °C, 94 %; d) H_2, Pd/C, 92 %; e) polyphosphoric acid, 80 °C, 85 % (95 % brsm); f) 1 N NaOH, 1,4-dioxane, reflux; g) BnBr, K_2CO_3, DMF, 95 % (over 2 steps); h) allyl bromide, NaH, THF/HMPA, 0 °C→RT, 80 %; i) BCl_3, CH_2Cl_2, −78 °C, 99 %; j) PIDA, MeOH, 0 °C. Bn = benzyl, brsm = based on recovered starting material, DMF = *N*,*N*-dimethylformamide, HMPA = hexamethylphosphoric triamide, Ms = methanesulfonyl, PIDA = (diacetoxyiodo)benzene, TEA = triethylamine, THF = tetrahydrofuran.

dimethoxy-1-tetralone,[8] mesylate **6** was converted to **8** in 59 % overall yield. Because tetralone **8** was not suitable for C,C-diallylation, the mesyl group was replaced with a benzyl group in two steps.[9] Diallylation of the benzyl derivative **9** (allyl bromide, NaH) was successful and gave ketone **10** in 80 % yield. Removal of the benzyl group with BCl_3 afforded phenol **11** in quantitative yield. Dearomatization of phenol **11** with $PhI(OAc)_2$ in MeOH generated MOB **12**, which turned out to be very labile toward spontaneous dimerization.[10] The dimer **13** was heated to 220 °C in mesitylene with the expectation of initiating a retro-Diels–Alder/intramolecular Diels–Alder process,[11] but the desired product was not observed.

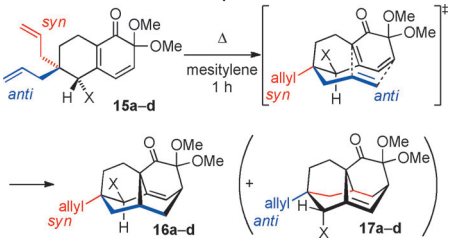
We postulated that the failure of the REDDA reaction of MOB **12** was a result of an extremely reactive conjugated enedione structure and/or an unfavorable conformation for the REDDA reaction because of the presence of the sp^2-hybridized C-10. Thus, several MOBs that include the sp^3-hybridized C-10 were prepared (Scheme 4). Reduction of ketone **11** with DIBAL gave benzyl alcohol **14b**. Treatment of **14b** with triethylsilane or methanol under acidic conditions afforded **14a** or **14c**, respectively. Silyl etherification of **14b** and selective deprotection with aqueous NaOH gave TES ether **14d**. Compounds **14a–d** were subjected to oxidative dearomatization with $PhI(OAc)_2$ in MeOH to afford REDDA precursors **15a–d**. As expected, we observed no dimerization of these MOBs during the oxidation reaction and purification.[12]

With precursors **15a–d** in hand, the REDDA reaction was carried out (Table 1). Heating of deoxy MOB **15a** in



Scheme 4. Preparation of alkoxy-substituted precursor. a) DIBAL, CH_2Cl_2, −78 °C, 91 %; b) Et_3SiH, TFA, THF, 0 °C→RT, 70 %; c) H_2SO_4, MeOH, 89 %; d) TESCl, imidazole, DMAP, CH_2Cl_2; e) 1 N NaOH, THF, 73 % (over 2 steps); f) PIDA, MeOH, 0 °C, respective yields: **15a** (66 %), **15b** (80 %), **15c** (quantitative), **15d** (92 %). DIBAL = diisobutylaluminum hydride, DMAP = *N*,*N*-4-dimethylaminopyridine, TES = triethylsilyl, TFA = trifluoroacetic acid.

Table 1: REDDA reaction with alkoxy-substituted MOB.



Entry	Substrate	X	*T* [°C]	Yield [%]	Ratio (**16**/**17**)[a]
1	**15a**	H	180	–[b]	–
2	**15b**	OH	180	36	3:2
3	**15c**	OMe	180	74	5:1
4	**15d**	OTES	180	85	>20:1
5	**15d**	OTES	150	62	>20:1
6	**15d**	OTES	200	83	10:1

[a] The ratio was determined by ^1H NMR spectroscopy. [b] Decomposition occurred.

mesitylene in a sealed tube (180 °C, 1 h; Table 1, entry 1) resulted in decomposition of the starting material. When hydroxy MOB **15b** was heated (Table 1, entry 2), the dimer was obtained as the major product along with a small amount of **16b** and **17b** (36 %, 3:2). However, the desired cycloadduct **16c** was obtained in 74 % yield by heating methyl ether **15c** (ca. 5:1 ratio of **16c** to **17c**; Table 1, entry 3). Finally, we found that the REDDA reaction of silyl ether **15d** (180 °C; Table 1, entry 4) afforded tetracyclic **16d** in high yield and almost as a single diastereomer. We reasoned that the steric repulsion between the bulky TESO group and the *syn* allyl group might force the *anti* allyl group to adopt a favorable conformation for the desired intramolecular reaction.

The structure of tetracyclic **16d** was determined by NMR spectroscopy.[13] Removal of the TES group of **16d** (TBAF, THF) afforded crystalline **16b**. Subsequent X-ray crystallographic analysis of **16b** (Figure 1)[14] confirmed the anti-Bredt tetracyclic skeleton.[15] This result established that we had achieved the first artificial synthesis of the tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]tridecane skeleton.

We subsequently proceeded to the construction of the pentacyclic skeleton of **1**, despite the lack of functionality at C-6 (Scheme 5). Addition of allylmagnesium bromide to ketone **11** gave triene **18** in excellent yield. Oxidative

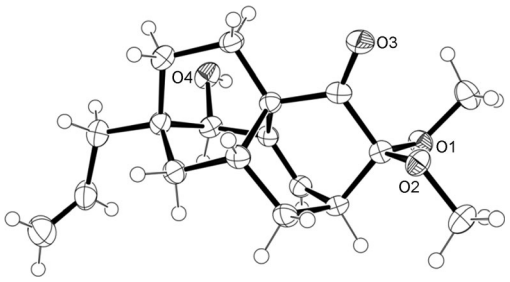
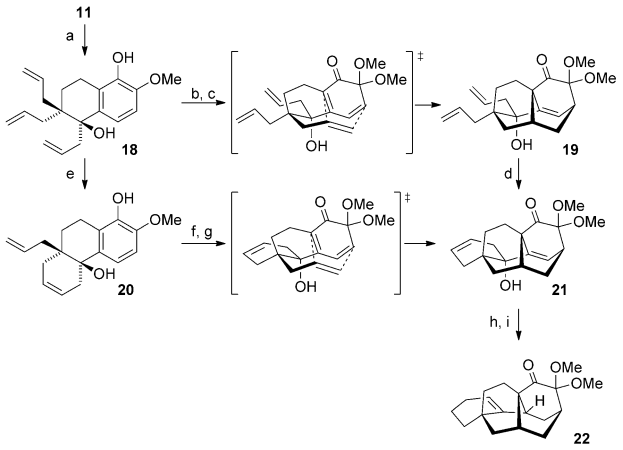


Figure 1. ORTEP drawing of **16b** (ellipsoids drawn at 50% probability).



Scheme 5. Construction of the pentacyclic skeleton of atropurpuran. a) AllylMgBr, THF, 0°C, 96%; b) PIDA, MeOH, 0°C, 89%; c) mesitylene, 180°C, 1 h, 79%; d) Grubbs' II catalyst, CH_2Cl_2, 99%; e) Grubbs' II catalyst, CH_2Cl_2, 56%; f) PIDA, MeOH, 0°C, 78%; g) mesitylene, 180°C, 1 h, 75%; e) H_2, $Pd(OH)_2/C$, THF, 78%; f) Tf_2O, pyridine, CH_2Cl_2, 85% (99% brsm). Tf = trifluoromethanesulfonyl.

dearomatization of **18** with PIDA followed by the REDDA reaction of the resulting MOB afforded tetracyclic adduct **19** as a single diastereomer. Treatment of **19** with Grubbs' second-generation catalyst provided the desired pentacyclic skeleton **21** in excellent yield. Alternatively, triene **18** was treated with Grubbs' second-generation catalyst to give *cis*-hydrophenanthrene **20** as a major product.[16] Oxidation of **20** with PIDA and the REDDA reaction of the tricyclic MOB was achieved to construct the same pentacyclic compound **21**. Finally, hydrogenation of **21** (H_2, $Pd(OH)_2/C$) and subsequent dehydration with Tf_2O and pyridine afforded **22** to complete the construction of the pentacyclic framework of **1**.

In summary, we have achieved the construction of the pentacyclic framework of atropurpuran by an intramolecular REDDA reaction. Characteristic features of the present study are: 1) the first synthesis of a tetracyclo[5.3.3.$0^{4,9}$.$0^{4,12}$]-tridecane skeleton and 2) a concise approach to the atropurpuran skeleton. These results demonstrate the power of the REDDA reaction by using MOB for the construction of anti-Bredt and cage-like complex molecules. Use of this methodology in synthetic efforts toward atropurpuran is currently underway.

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[9] Mesyl protection is quite important for the effective conversion to tetralone **9**. The overall yields from benzyl ether or *o*-eugenol itself were 31% and 20%, respectively.
[10] Formation of dimer **13** was confirmed by LRMS and ^{1}H NMR spectroscopy. However, the stereochemistry of dimer **13** was not confirmed.
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[13] See the Supporting Information.
[14] CCDC 827527 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.
[15] A torsion angle of 146.3° for the C10–C9–C11–C12 bonds is consistent with our previous observation on an *E*-olefin that contains an eight-membered ring, see: R. Matsui, K. Seto, K. Fujita, T. Suzuki, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2010**, *122*, 10266–10271; *Angew. Chem. Int. Ed.* **2010**, *49*, 10068–10073.
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