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A new, chiral aminoanthracene for the Diels–Alder/retro-Diels–Alder sequence in lactam and butenolide synthesis

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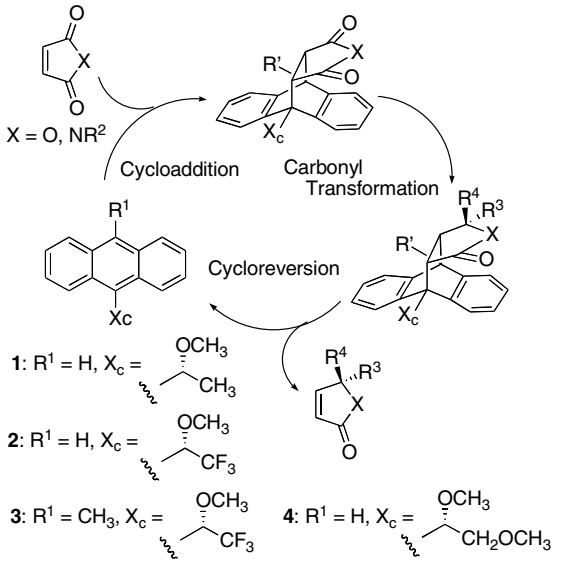
Abstract—9-(2-Phenylethyl)aminoanthracene has been prepared and used as a template in the Diels–Alder/retro-Diels–Alder sequence to produce α,β-butenolides and α,β-unsaturated lactams. In this sequence the aminoanthracene serves as a stereo- and regio-controlling chaperone in guiding maleic anhydride or *N*-alkylmaleimides through transformations to the butenolide or lactam targets.

For the past several years we have been exploring anthracenes substituted at C9 with a stereogenic center as chiral templates for use in Diels–Alder/retro-Diels–Alder sequences[1,2] for the purpose of transforming maleic anhydride and *N*-alkylmaleimide cycloadducts into α,β-butenolides and α,β-unsaturated lactams (Scheme 1). Such a sequence requires a highly diastereoselective initial cycloaddition, followed by regio- and stereoselective transformation of one of the carbonyl groups of the mounted dienophile. In this approach, the chiral anthracene template serves as the stereocontrolling element in both the cycloaddition and subsequent carbonyl chemistry, and must also control the regiochemistry in the latter reactions.

Initially we examined the diastereoselectivity of (*S*)-9-(1-methoxyethyl)anthracene (**1**) and (*R*)-9-(1-methoxy-2,2,2-trifluoromethyl)anthracene (**2**, Pirkle's alcohol) in cycloadditions with maleic anhydride and *N*-methylmaleimide.[3] While both of these anthracene templates worked well in cycloadditions, **1** was unstable to prolonged storage, producing detectable amounts of anthraquinone via oxidation under ambient conditions, and **2** was less reactive in the cycloadditions toward other dienophiles.



Scheme 1.

With these results in hand, we then prepared a second generation of chiral anthracene templates:[4] (*R*)-10-methyl-9-(1-methoxy-2,2,2-trifluoroethyl)anthracene (**3**),[5] (*R*)-9-(1,2-dimethoxyethyl)anthracene (**4**),[6] (*R*)-9-(1-phenylethyl)aminoanthracene (**5**),[4] and the homochiral 9-acyloxyanthracenes **6a** and **6b** for use in the Diels–Alder/retro-Diels–Alder sequence. Placement of the methyl group at C10 in **3** (Scheme 1 above) improved the reactivity in cycloadditions relative to **2** by a factor of 10, and

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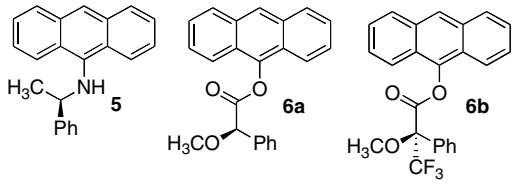
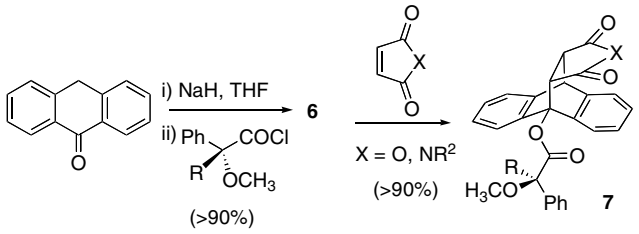
this anthracene was used as a template in a Diels–Alder/retro-Diels–Alder sequence to prepare the butenolide precursor to a rove beetle pheromone.[5] The cycloreversion was accomplished by heating to 200 °C under vacuum. However, this enhanced reactivity came at the expense of regioselectivity in the carbonyl reduction as well as in the cycloaddition with nonsymmetric dienophiles such as 5-acetoxyfuranone.[4,5]



Homochiral dimethoxyethylanthracene **4** (Scheme 1 above) also underwent cycloadditions with a variety of maleic anhydrides and *N*-alkylmaleimides with exclusive diastereoselectivity, shown to be under kinetic control. Regioselectivity in the carbonyl transformations was also exclusive, with flash vacuum pyrolysis (FVP) at 400 °C furnishing α,β-unsaturated lactams in good yields, including indolizidone bicyclic systems.[6] Jones has also probed the cycloadditions of chiral anthracenes.[7]

In an effort to reduce the temperature required for the cycloreversion, we also prepared homochiral anthracenes **5**, **6a**, and **6b**. Czarnik has shown that electron donating substituents at C9 (and C10) of anthracene cycloadducts accelerate the cycloreversion,[8] thus we anticipated that cycloadducts of **5** should undergo cycloreversion at lower temperatures in comparison to **4**. Esters **6a** and **6b** were also examined since Trost,[9] Thornton[10] and others[11] had shown that mandelate-type acyloxy substitution at C1 of butadienes can indeed lead to excellent diastereoselectivity in cycloadditions. Basic cleavage of the ester group should then lead to a rapid oxyanion promoted cycloreversion, as demonstrated by both Knapp[12] and Nicolaou.[13]

Trapping the oxyanion produced by treating anthrone with NaH with the appropriate acid chloride produced **6a** and **6b** in excellent yields (>90%, Scheme 2). Both anthracenes were stable to storage. Unfortunately, cycloadditions with maleic anhydride and *N*-methylmaleimide with **6a**, and the latter dienophile with **6b** produced mixtures of diastereomers of **7** in 3:2 ratios from **6a**, and a 1.2:1 ratio from **6b**. Lewis acid catalysis failed to improve the ratios, so these anthracenes were no longer pursued.

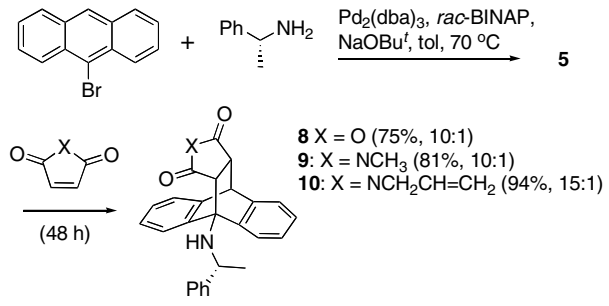


Scheme 2.

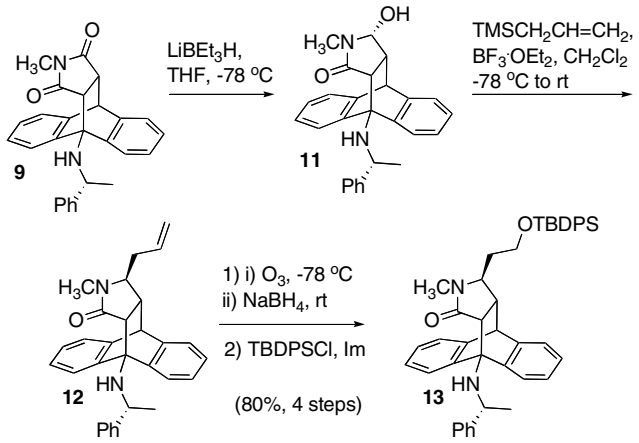
Our attention then turned to homochiral aminoanthracene **5**. Rawal has demonstrated the effectiveness of homochiral 1-aminobutadienes in controlling the stereochemistry in cycloadditions,[14] so it was anticipated that cycloadditions of **5** would also proceed with high diastereoselectivity. Aminoanthracene **5** was readily obtained by Pd-catalyzed aryl amination of 9-bromoanthracene with (*R*)-1-phenylethylamine (Scheme 3).[4,15] As anticipated, this aminoanthracene oxidized under ambient conditions,[16] but could be stored under nitrogen at 0 °C. Alternatively, **5** could be easily trapped by acetylation to give the corresponding *N*-acetate (53%, two steps), but this *N*-acetylaminoanthracene proved to be unreactive in cycloadditions with maleic anhydride and *N*-methylmaleimide (NMM). More importantly, **5** could also be trapped as the cycloadduct immediately after preparation by the addition of maleic anhydride or *N*-alkylmaleimide under nitrogen at room temperature. Though slow (48 h), cycloadducts **8**–**10** were isolated in good to excellent yields and with high diastereoselectivities (⩾10:1), though in contrast to anthracenes **1**–**4**, which underwent cycloadditions with maleic anhydride and *N*-alkylmaleimides with exclusive diastereoselectivity, the minor diastereomers were detected in each case.[17] The cycloadditions occurred much more rapidly at higher temperatures, but led to an increased amount of minor diastereomer. The assignment of the stereochemistry of the cycloadducts is described below.

With the cycloadducts in hand, the regioselectivity of carbonyl transformations was then probed beginning with adduct **9** (Scheme 4). Reduction with Super-Hydride occurred only at the carbonyl remote to the amino group, leading to acyl aminal **11**, which was allylated without further purification to lactam **12** (68%, two steps). Ozonolysis with $NaBH_4$ workup (91%), with subsequent TBDPS protection yielded **13** (77%). This four-step sequence could also be performed without purification of the intermediates, giving **13** in 80% overall yield from **9**.

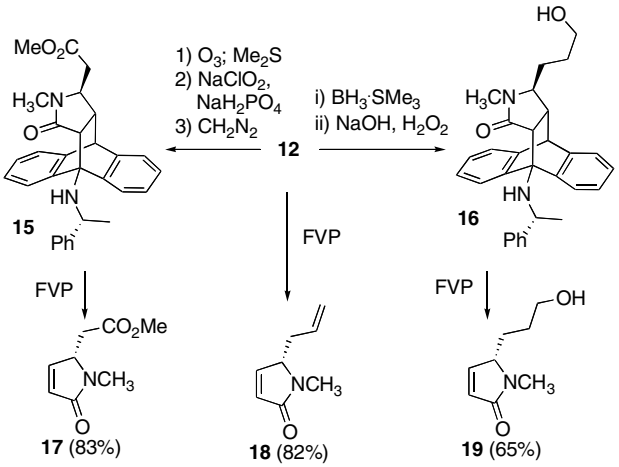
Conditions to accomplish the cycloreversion with **13** were then examined, using both microwave irradiation[18] and the more classic flash vacuum pyrolysis.[19] After considerable experimentation it was discovered that microwave irradiation of a solid mixture of **13** and



Scheme 3.



Scheme 4.



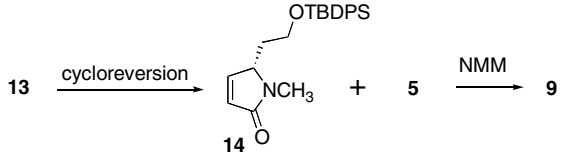
Scheme 6.

NMM[20] at 160 °C (3 min) gave a 57% yield of lactam **14** along with 67% yield of adduct **9**, though the latter only with a diastereoselectivity of 2:1 (Scheme 5). Presumably the higher temperature required for the cycloreversion results in a hemorrhaging of the diastereoselectivity of the cycloaddition when trapping aminoanthracene **5** in situ, as previously noted with the thermally promoted cycloadditions. Microwave irradiation at 140 °C led to only 10% cycloreversion, while longer irradiation at 160 °C reduced the yield of **14**. Microwave irradiation on various solid supports was also unsuccessful.

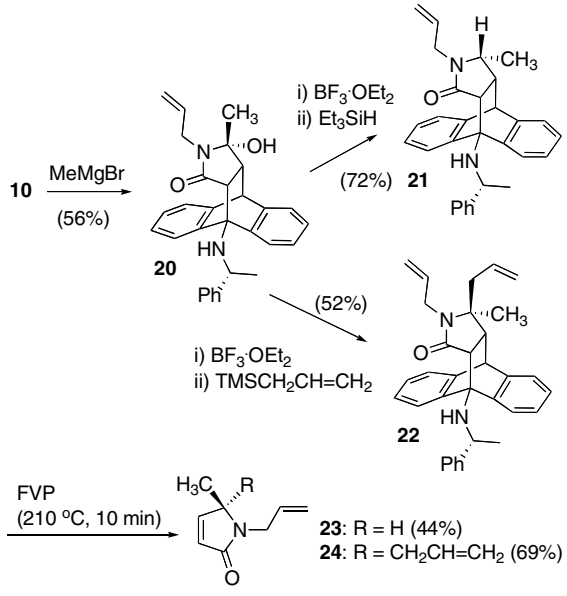
Given the somewhat disappointing results of the microwave-promoted cycloreversion (modest yield and poor diastereoselectivity in trapping **5**), flash vacuum pyrolysis was also examined. Heating **13** at 190 °C at 2 mmHg (10 min) gave a 74% yield of **14**, recovered in a trap cooled to −78 °C. Aminoanthracene **5** condensed on the sides of the exit tube after emerging from the tube furnace, and could be recovered by washing with toluene, then adding NNM to give **9** (70%).

Cycloreversion via FVP under the same conditions on lactam **12**, or following routine transformations of **12** to related derivatives, also proceeded comparably to produce **17**–**19** (Scheme 6, FVP 190 °C, 10 min). In each case, aminoanthracene **5** could be trapped as NMR adduct **9** as described above in a minimum of 70% yield. Of note in these examples is the successful cycloreversion of **16** without alcohol protection.

Methyl Grignard addition to *N*-allylmaleimide cycloadduct **10** also occurred solely at the carbonyl remote to the chiral amino substituent to give **20**, a regioselectivity analogous to that observed in Grignard additions to other chiral anthracenes.[4,6] Some retro-Diels–Alder products were also observed in this reaction, accounting for the relatively modest yield of 56%. Allylation and silane reduction to **21** and **22**, respectively, then FVP gave lactams **23** and **24** (Scheme 7).

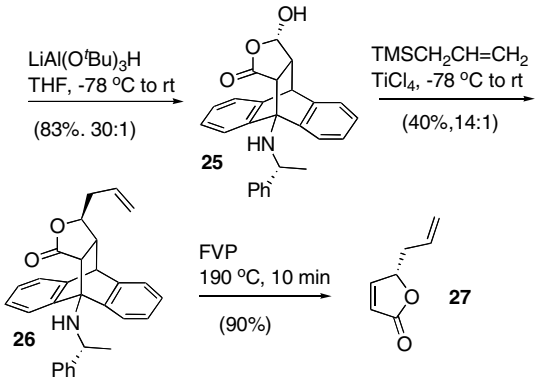


Scheme 5.



Scheme 7.

The known allylated butenolide **27** was also prepared in analogous fashion beginning with the maleic anhydride cycloadduct **8** (Scheme 8). Stereoselective reduction of **8** (83%), followed by $TiCl_4$ catalyzed allylation (40%, 14:1) gave lactone **26**. Flash vacuum pyrolysis under the standard conditions gave butenolide **27** in 90% yield, and 97.4% ee as established by chiral GC.[21] Comparison of the $[\alpha]_D$ +94 (*c* 3.0, CH_2Cl_2) with that reported in the literature (+105 *c* 4.1, CH_2Cl_2)[22] allowed for the assignment of the absolute stereochemistry of **27**, and in turn, the precursors **25** and **26**. Furthermore, since it is presumed that the stereocontrol for the cycloadditions of maleic anhydride and the *N*-alkylmaleimides is the



Scheme 8.

same, the stereochemistry of the maleimide cycloadducts **9** and **10**, as well as the α,β-unsaturated lactams **14**, **17**–**19**, **23**, and **24** were assigned as shown earlier. The high ee value for **27** confirms that racemization did not occur during the pyrolysis. The trace amount of the enantiomer results from the less than absolute diastereoselectivity in the original cycloaddition.

In competition cycloadditions with unsubstituted anthracene and NMM, **5** proved to be six times as reactive. Thus, the reactivity of **5** is comparable to that of **1** and **3**,[3] and about twice as reactive as 4.[6]

In conclusion, a new, homochiral anthracene (**5**) has been prepared and examined in the Diels–Alder/retro-Diels–Alder sequence for the preparation of α,β-unsaturated lactams and α,β-butenolides. While **5** was successful in this sequence, three main areas for improvement were defined. First, a faster, highly diastereoselective Diels–Alder reaction needs to be achieved. This objective may be attained if an aminoanthracene is available that undergoes the cycloadditions at higher temperatures yet still maintains high diastereoselectivity. Indeed, **5** proved to be less stereoselective in its cycloadditions than chiral anthracenes **1**–**4**. Second, an aminoanthracene, which yields cycloadducts that are stable to Grignard additions (avoids cycloreversion) needs to be discovered. Finally, while the retro-Diels–Alder reactions were successful at 190 °C, a considerable improvement over earlier attempts, achieving the cycloreversion at lower temperatures remains a target. We are currently examining other aminoanthracenes that may accomplished these goals.

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17. Operationally, the coupling mixture containing crude **5** was filtered through Celite, washing with anhydrous ether. After evaporation of the solvent in vacuo, the residue was dissolved in anhydrous toluene and the solution was added dropwise to the solid dienophile (NMM or maleic anhydride, 1.2 equiv). The final concentration of **5** was 0.3 M. The solution was maintained under nitrogen at rt.
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20. This solid mixture was prepared by dissolving **13** with NMM (5 equiv) in CH_2Cl_2, then removing the solvent in vacuo.
21. Chromatography was performed on a Shimadzu GC-17A chromatograph equipped with an autosampler, GANNA DEX-225 capillary column (Supelco, 30 m × 0.25 mm × 0.25 μm); flow rate 1 mL/min with He carrier gas; separation factor (α) = 25.
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