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Enantioselective syntheses of candenatenins B and C using a chiral anthracene auxiliary

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ABSTRACT

The asymmetric syntheses of two anticancer natural products, candenatenins B and C, are described, leading to a revision of the originally assigned stereochemistries. The syntheses follow a Diels–Alder/retro-Diels Alder strategy using a chiral anthracene auxiliary to access both targets with 90% ee. The inherent structural qualities of the auxiliary allow for both regio- and diastereoselective transformations.

The use of chiral anthracene derivatives as stereocontrolling auxiliaries in Diels–Alder/retro Diels–Alder (DA/rDA) sequences has the potential to become a useful tool for asymmetric synthesis.[1–3] By tailoring the auxiliary so that one hemisphere contains a stereogenic center adjacent to the anthracene core while the other remains unobstructed, one can control not only the diastereoselectivity of the initial cycloaddition, but also the selectivities of subsequent transformations of functional groups originating from the dienophile. Our group,[2] as well as that of Jones,[3] have reported the use of chiral 9-substituted anthracenes **1–3** (Fig. 1) in highly diastereoselective Diels–Alder cycloadditions with maleimide and related dienophiles. Further transformations, including carbonyl reductions (Scheme 1, Eq. 1)[2a] and Grignard additions (Scheme 1, Eq. 2)[2b] were achieved with complete regioselectivity at the carbonyl remote to the anthracene-derived stereogenic center, with a diastereoselective approach of the Grignard reagents occurring solely from the more accessible top face of the cycloadduct. Release of the transformed dienophile could then be achieved by a retro Diels–Alder (rDA) reaction,[2b–f,3a,c,4,5] to give enantioenriched heterocycles such as **9** (Scheme 1, Eq. 3).[2d]

Based on these results, we considered the application of other dienophiles in this DA/rDA methodology, specifically *p*-benzoquinone. Knapp has previously applied a DA/rDA strategy with an achiral anthracene template as an alkene protecting group with *p*-benzoquinone as the dienophile in his synthesis of *rac*-conduritol.[6] Thus, we felt that a homochiral anthracene template should

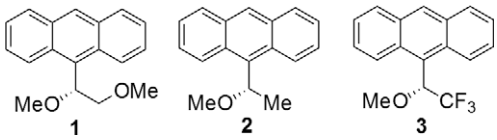

Figure 1. 9-Substituted chiral anthracene auxiliaries.

successfully function as a stereocontrolling element in the DA/rDA sequence with *p*-benzoquinone dienophiles in the syntheses of enantioenriched, chiral 4-substituted cyclohexenones (Scheme 2). In this strategy, a cycloaddition between **2** and **10**, with subsequent regioselective carbonyl transformation of cycloadduct **11** followed by a cycloreversion would allow access to the target 4-substituted cyclohexenones **13** in highly enantioenriched form. Several examples of this structural motif are found in the recently discovered candenatenins B–D **14–16** (assigned structures, Fig. 2).[7] These compounds were isolated from the heartwood of *Dalbergia candenatensis* and both **14** and **15** showed modest levels of activity against an HT-29 colon cancer cell line (17.8 and 19.7 μM, respectively), though this anticancer activity was also shown to be a consequence of the promiscuous α,β-unsaturated carbonyl functionality. The single remote stereogenic centers of **14–16** are tertiary alcohols, which we have previously shown are accessible via regioselective Grignard addition to dicarbonyl-containing cycloadducts of chiral anthracenes, making these natural products ideal targets for our ongoing studies in the use of chiral anthracene auxiliaries. Another important goal in this work was to find a procedure which accomplished the cycloreversion without the

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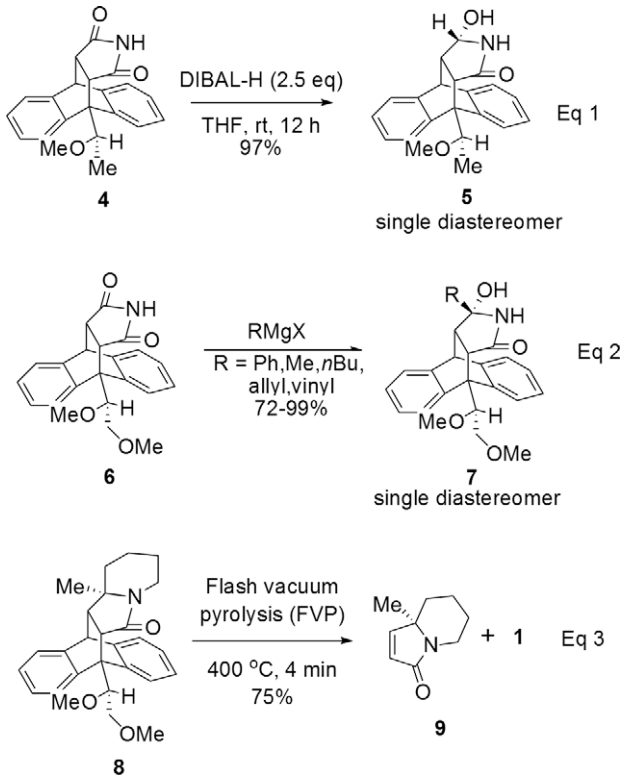
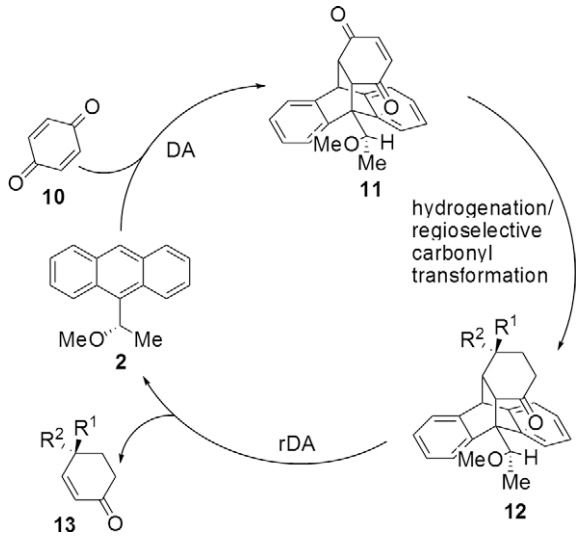


Scheme 1. Transformations of chiral anthracene cycloadducts.



Scheme 2. Synthetic plan to access homochiral 4-substituted cyclohexenones.

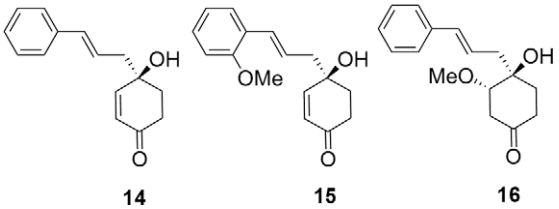


Figure 2. Structures of candenatenins B–D **14**–**16**.

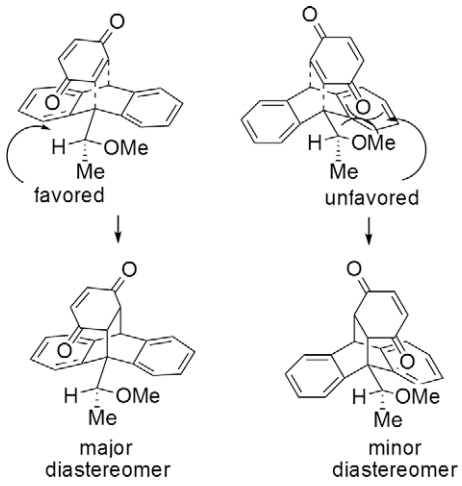
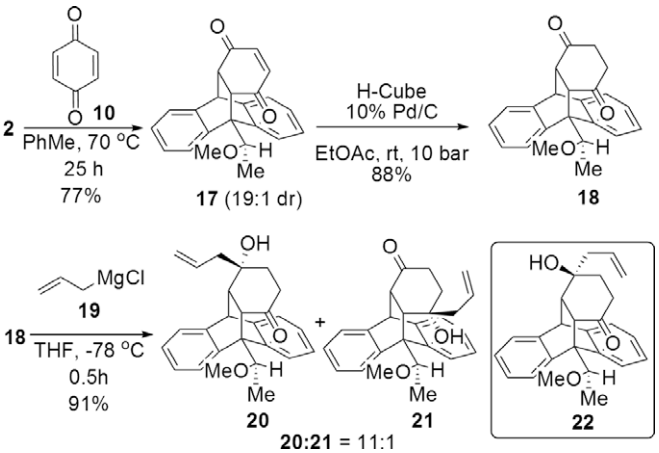


Figure 3. Transition state models to explain diastereoselectivity.[8]

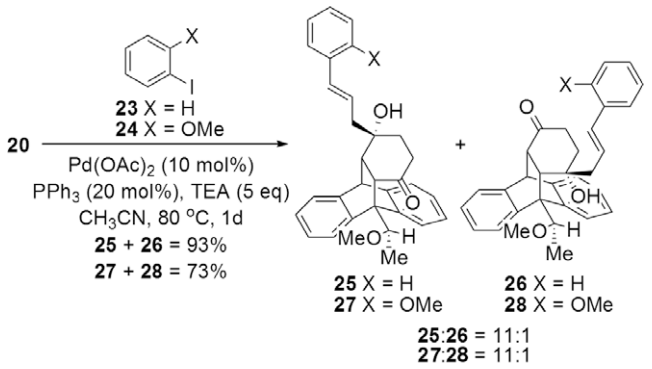
need to resort to flash vacuum pyrolysis, a methodology which severely restricts application of the DA/rDA strategy.

The highly diastereoselective cycloaddition of *ent*-**2** with **10** has been reported by Jones and co-workers,[8] and we had also observed similar diastereoselectivity with **2**.[4] In Jones' work, optimized conditions produced the desired cycloadduct in 67% yield and a diastereomeric ratio (dr) of 96:4. The proposed basis for this selectivity was suggested to be the unfavorable electrostatic repulsion between the lone pairs on the carbonyl and methoxy oxygen atoms in the unfavored transition state (Fig. 3).[8] Recent theoretical studies by Aviyente and co-workers[9] have supported this basis of stereoselectivity in the cycloadditions of **2** with maleic anhydride.

Our synthesis began with the diastereoselective cycloaddition of **2** (97.5% ee)[10] and **10**, yielding **17** (77% yield, 19:1 dr,[11] Scheme 3). Hydrogenation with 10% Pd/C using an H-Cube® reactor on a 100 mg scale gave **18** in 88% isolated yield. Regioselective Grignard addition to **18** with allylmagnesium chloride **19** should then establish the single stereocenter present in the natural products. While this reaction did proceed in 91% yield at low temperature, an 11:1 mixture of inseparable regioisomers was isolated, in contrast to the production of a single isomer in the analogous allyl Grignard addition to maleimide cycloadducts **4**[4] and **6**.[2b] The major product was determined to be **20**,[12] as expected. The minor product, which could not be purified in sufficient amounts for independent structure assignment, was assumed to be regioisomer **21**, resulting from addition to the carbonyl closer to the original anthracene



Scheme 3. Synthesis of cycloadduct **20**.



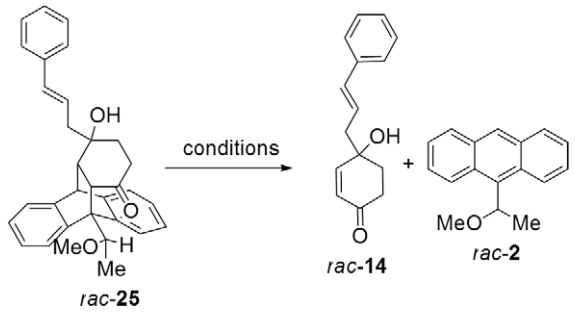
Scheme 4. Heck coupling of allyl cycloadduct **20**.

stereogenic center, rather than diastereomer **22** (Scheme 3, inset), which would result from allyl Grignard addition to the bottom face of the same carbonyl as in the production of **20**, as this is a very unfavorable mode of addition for steric reasons.

A Heck coupling[13] was then performed to install the aryl rings found in the natural products (Scheme 4). These reactions proceeded readily with no detection of the (*Z*)-alkene. However, separation of the minor regioisomer from the previous Grignard addition step was still not achieved, so the combined material was carried through to the final step.

With cycloadducts **25** and **27** in hand, the retro Diels–Alder (rDA) cycloreversion was investigated. Previously, flash vacuum pyrolysis at 400 °C was required to achieve good yields of product and fully recover the chiral anthracene auxiliary.[2b–f,3a,4] While effective, this methodology is not attractive due to the special nature of the apparatus needed as well as the extremely high temperature. Refluxing in high boiling solvents has also been employed for rDA reactions from anthracene diene systems.[2b–d,4,5b] However, recent reports have shown that microwave irradiation in DMSO for 5 min has also been effective at promoting rDA reactions.[4,14] Using racemic cycloadduct **25** as a test substrate, several conditions were screened to determine the optimal parameters for cycloreversion (Table 1). At temperatures less than or equal to 135 °C, minimal conversion (⩽30%) was observed under both microwave irradiation (entries 1–3) and conventional oil bath heating conditions (entry 7). Addition of stoichiometric amounts of a Lewis acid ($Sc(OTf)_3$) gave higher conversion at 135 °C (60%), but some decomposition products were also noticed (entry 4). By changing the solvent to 1,2-dichlorobenzene (entries 5 and 8) or DMSO (entry 6) without Lewis acid catalysis,[4,14] at higher temperatures, higher conversions were achieved. Based upon this study, the conditions chosen for cycloreversion were microwave irradiation at 180 °C using 1,2-dichlorobenzene as solvent, which can be easily removed from the crude reaction mixture during chromatography.

Table 1
Condition screening for the cycloreversion

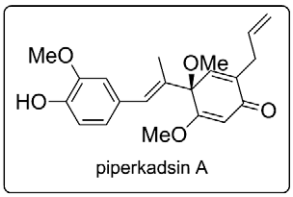


Entry	Conditions	Solvent	% Conv.[a]
1	μW, 75 °C, 300 W, 10 min	Chlorobenzene	0
2	μW, 85 °C, 300 W, 10 min[b]	Chlorobenzene	10
3	μW, 135 °C, 300 W, 20 min	Chlorobenzene	20
4	μW, 135 °C, 300 W, 20 min[b]	Chlorobenzene	60[c]
5	μW, 180 °C, 200 W, 20 min	1,2-Dichlorobenzene	100
6	μW, 230 °C, 150 W, 5 min	DMSO	100
7	135 °C, 18 h	Chlorobenzene	30
8	180 °C, 2.5 h	1,2-Dichlorobenzene	80[c]

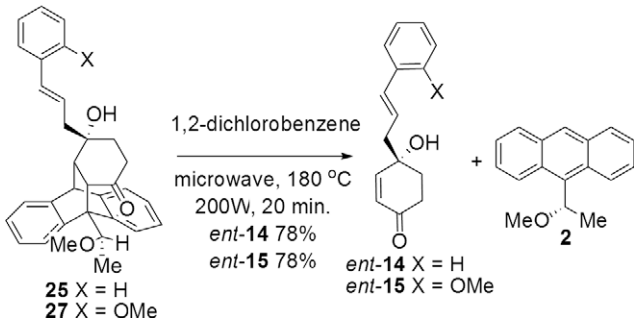
[a] Based upon TLC and/or crude NMR analysis.
[b] With 1.0 equiv $Sc(OTf)_3$ additive.
[c] Decomposition products also detected.

Enantioenriched cycloadducts **25** and **27** were then subjected to the optimized cycloreversion conditions, yielding the enantiomers of the natural products, *ent*-**14** and *ent*-**15**, both in 78% yield (Scheme 5), along with 85% recovery of the chiral anthracene (a small amount of anthrone was also detected by TLC from oxidation of the chiral anthracene under the high temperature conditions).

Chiral HPLC analysis of *ent*-**14** indicated 90% ee, in accordance with the 97.5% ee of the original chiral anthracene **2**, and the small quantities of the inseparable minor regioisomer from the allyl Grignard addition yielding the opposite enantiomer upon cycloreversion. The synthetic compounds had ^1H and ^{13}C NMR spectroscopic data identical to the literature report.[7] However, the sense of optical rotation was the same as that reported in the literature,[15] although the synthesized compounds have the opposite configuration based on the chiral anthracene used and the outcome of the ensuing regio- and diastereoselective transformations. Therefore, the synthetic compounds share the same configuration as the natural products and the original stereochemical assignment of candenatenins B and C should be revised to (*S*). The original assignment of the absolute stereochemistry of candenatenin B **14** was based on a CD comparison with that of the natural product piperkadsin A (*Inset*).[16] Such a comparison for absolute stereochemical assignment is not valid since the chromophores of piperkadsin A are significantly different from that of **14**.



In conclusion, the syntheses of two anticancer natural products, candenatenins B and C, have been achieved using a DA/rDA strategy with a chiral anthracene auxiliary. The synthetic compounds were produced in 90% ee and good yields over a 5-step linear sequence (42% and 33% overall yields for B and C, respectively).



Scheme 5. Cycloreversion of cycloadducts **25** and **27**.

The sense of optical rotation of the synthesized compounds led to a revision of the originally assigned stereochemistry of the natural products. The high-yielding and highly selective nature of the DA/rDA strategy employing chiral anthracene templates as stereocontrolling elements make this an attractive methodology for asymmetric synthesis. In this example, a facile synthesis of chiral 4-substituted cyclohexenones, which historically have proven challenging to obtain in highly enantioenriched form,[17] has been achieved. Future plans are aimed at applying this methodology to more complex natural products and natural product-based scaffolds, in particular focusing on cyclohexenones with stereogenic centers at C4.

Acknowledgments

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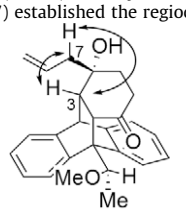
11. All isomeric ratios determined by crude NMR and/or UPLC.
12. Determined by 2D NMR spectroscopy in $CDCl_3$: key HMBC correlations between bridge proton H-3 (δ 2.41) and allylic carbon C-7 (δ 45.2) as well as H-7 (δ 2.47) and C-3 (δ 52.7) established the regiochemistry of **20**.



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