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Intramolecular Cyclobutadiene Cycloaddition/Cyclopropanation/Thermal Rearrangement: An Effective Strategy for the Asymmetric Syntheses of Pleocarpenene and Pleocarpenone

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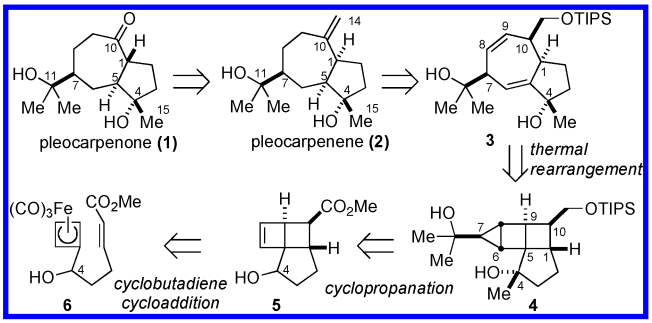
The introduction of new methods for accessing functionalized medium ring-containing compounds more efficiently remains a valuable objective.[1] We have developed an intramolecular cycloaddition of cyclobutadiene[2] followed by cyclopropanation and rearrangement as an effective approach for the stereospecific preparation of bicyclo[5.3.0]decane ring systems.[3] Herein, we describe the first application of this strategy in the asymmetric preparation of pleocarpenone (**1**) and pleocarpenene (**2**), two guaiane natural products isolated in 1976 from *Pleocarphus revolutus*.[4]

Our approach to these natural products is summarized in Scheme 1. Since pleocarpenone is accessible through the ozonolysis/epimerization of pleocarpenene,[4c] both natural products could arise from cycloheptadiene **3**. Intermediate **3**, with the appropriate relative stereochemistry at C1, C4, and C7, should be available through a thermal rearrangement of cyclopropane **4**.[3a] The requisite, highly strained precursor **4** would be generated through a diastereoselective cyclopropanation of cyclobutene **5** followed by further functionalization. An intramolecular Diels−Alder with either racemic or enantiomerically enriched cyclobutadiene **6** would be used to generate cyclobutene **5**.[2]

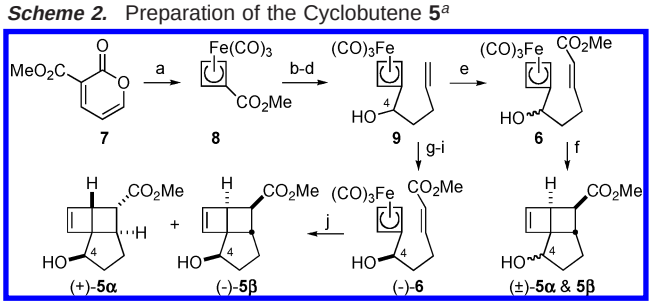
Scheme 1. Retrosynthesis of Pleocarpenone and Pleocarpenene



An improved preparation of racemic and enantiomerically enriched cyclobutene **5** is described in Scheme 2. The synthesis was initiated by a photochemical electrocyclization of commercially available α-pyrone **7**, followed by addition of $Fe_2(CO)_9$, to generate the iron cyclobutadiene methyl ester **8** in a single operation.[2c] Reduction of iron complex **8** with DIBAL, followed by oxidation of the resulting alcohol, yielded an aldehyde that upon treatment with 3-butenyl magnesium bromide provided alcohol (±)-**9**. Cross-metathesis of the terminal olefin of **9** with methyl acrylate (in the presence of 2.5 mol % of Hoveyda−Grubbs second generation catalyst **10**)[5e,f] generated the desired iron enone (±)-**6** in 94% yield with a 13:1 *E*:*Z* selectivity.[5] In this racemic route, cyclobutadiene was liberated by CAN oxidation to yield a 1:3.3 mixture of C4 alcohol diastereomers (±)-**5**α and (±)-**5**β in 91% yield.[2d] These isomers, which converge later in the synthesis, can be carried on as a mixture or as isolated intermediates.

The enantioselective route to (+)- and (-)-pleocarpenene requires the asymmetric preparation of compound **9**. Unfortunately, the

Scheme 2. Preparation of the Cyclobutene **5**[a]



[a] Reaction conditions: (a) *hν*, PhH; $Fe_2(CO)_9$, 64%; (b) DIBAL, Et_2O, 0 °C to rt, 95%; (c) MnO_2, CH_2Cl_2, 4 Å MS, 83%; (d) CH_2═$CHCH_2CH_2MgBr$, Et_2O, −78 °C, 96%; (e) CH_2═$CHCO_2Me$ (10 equiv), Grubbs' second cat. (**10**) (2.5 mol %), 60 °C, (94%, 13:1 *E*:*Z*); (f) CAN, acetone, (91%, 3.3:1 β:α); (g) MnO_2, CH_2Cl_2, 4 Å MS (90%); (h) catechol borane, (3a*S*)-tetrahydro-1-methyl-3,3,-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (**11**) (15 mol %), toluene, −78 °C (96%, 92% ee); (i) CH_2═$CHCO_2Me$ (10 equiv), **10** (2.5 mol %), 60 °C, (94%, 13:1 *E*:*Z*); (j) CAN, acetone; separation on 10 wt % $AgNO_3$ on silica gel (80%, 2.7:1 β:α).

asymmetric addition of 3-butenylzinc reagents to the corresponding cyclobutadieneiron tricarbonyl carboxaldehyde proceeded with poor conversion and low enantioselectivity.[6] Instead, the oxidation of compound **9**, followed by an asymmetric reduction of the resulting ketone with the (*S*)-B-Me-CBS-catalyst **11**, provided the enantioenriched alcohol (−)-**9** in 96% yield and 92% ee.[7] Again, cross-metathesis of (−)-**9** with methyl acrylate led to ester (−)-**6**, which upon oxidative cyclization provided the separable, enantioenriched cyclobutenyl diastereomers (−)-**5**β and (+)-**5**α in approximately 3:1 ratio. Each of these enantiomerically enriched diastereomers leads to a unique antipode of the natural product. Simply switching the CBS catalyst antipode then provides the enantiomer of these diastereomers, which in turn leads to the enantiomerically enriched final products in the opposite ratio.

As illustrated in Scheme 3, further functionalization was necessary to prepare cyclobutene **5** for cyclopropanation. Reduction of the methyl ester with LAH afforded diol **12**. An orthogonal one-pot, bishydroxyl protection was developed to yield the acylated secondary and silylated primary alcohol **13** in 87−89% yield (two steps). After screening a range of conditions, considerable stereochemical control was observed in the ethyl diazoacetate (EDA) cyclopropanation of cyclobutene **13** using $Cu(acac)_2$ as a catalyst. Additional optimization allowed for a one-pot cyclopropanation/deacetylation, generating the highly strained, cyclopropanated intermediate **14** as the sole observable diastereomer (i.e., >20/1) in 93−95% yield.[8]

The highly compact and rigid nature of cyclopropane **14** provided an opportunity for the stereocontrolled tailoring of the molecule's peripheral features. We envisioned that oxidation of the C4-hydroxyl group followed by addition of excess MeMgCl to the resulting keto ester should lead to diol **4** with the desired C4 stereochemistry.

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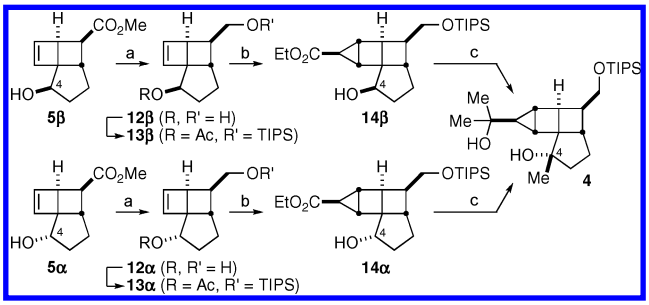
Scheme 3. Cyclopropanation of Cyclobutene **5**[a]

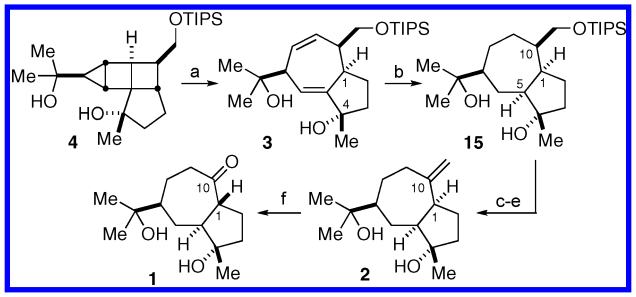


[a] Data shown for one enantiomeric series. Reaction conditions: (a) (i) LAH, THF, 0 °C to rt; (ii) TIPSCl, DMAP, Et_3N, THF, 4 Å MS; Ac_2O (87−89%); (b) EDA, $Cu(acac)_2$ (5 mol %), CH_2Cl_2, reflux; EtOH, rt; then $NaOEt_{(s)}$ (93−95%); (c) $(COCl)_2$, DMSO, THF, −62 °C; Et_3N, rt; MeMgCl, −78 °C (79−82%).

Since we had shown that carbonyl functionality adjacent to this strained ring system could lead to facile ring opening,[3b] a tandem oxidation/alkylation strategy was employed using procedures by Nubbemeyer and Ireland to generate compound **4** in 79−82% yield.[9]

We expected the thermal rearrangement of the highly functionalized cycloadduct **4** to yield the desired bicyclo[5.3.0]decane **3** with inversion of the C1 stereochemistry.[3a] Unfortunately, initial fragmentations led to significant levels of decomposition and low yields of the desired 5−7 ring system. Apparently, the acid-sensitive tertiary allylic alcohol (C4) in cycloheptadiene **3** was responsible for the poor outcome since addition of DBU rectified the problem.[10] As illustrated in Scheme 4, the optimized rearrangement provided the desired product **3** with inversion at C1 in 76% yield.

Scheme 4. Completion of the Total Synthesis[a]



[a] Reaction conditions: (a) benzene, 200 °C, DBU (15 mol %) (76%); (b) W.R. Grace 2800 RaNi, H_2 (100 atm), acetone, 63%; (c) TBAF, THF, 99%; (d) TsCl, Et_3N, DMAP, THF, CH_2Cl_2, 99%; (e) NaI, DBU, DMF, 80 °C, 83%; (f) O_3, MeOH, −78 °C; DMS, rt; NaOMe (85%).

Completion of pleocarpenene's synthesis required the reduction of cycloheptadiene **3** to generate compound **15** with the noted configuration at C5. While a variety of homogeneous hydrogenations were not successful,[11] heterogeneous methods did provide the desired product.[12] Optimal conditions were observed with Raney Nickel 2800 as catalyst, stirred in acetone under H_2 (100 atm) for 12 h to afford compound **15** in 63% yield.

With four stereogenic centers in place, dehydration of the protected alcohol remained to complete the synthesis. Removal of the TIPS group was accomplished with TBAF. Selective tosylation of the primary alcohol and elimination of the intermediate alkyl iodide afforded pleocarpenene **2** in 83% yield (99% ee, 70% yield after recrystallization).[13] Ozonolysis and epimerization of **2** yielded pleocarpenone **1**, which was spectroscopically identical to the naturally occurring material. In addition, the route allowed for confirmation of the absolute stereochemistry of these systems.

In summary, a new strategy for generating 5−7 ring systems has been employed in the first asymmetric total synthesis of pleocarpenene (**2**) and pleocarpenone (**1**). An intramolecular cycloaddition of cyclobutadiene followed by cyclopropanation and thermal rearrangement (**6** → **5** → **4** → **3**) are highlighted as the key steps in the synthesis.

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Supporting Information Available: Experimental procedures and data on new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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