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Intramolecular Diels–Alder Cycloadditions of Fulvenes. Application to the Kigelinol, Neoamphilectane, and Kempane Skeletons

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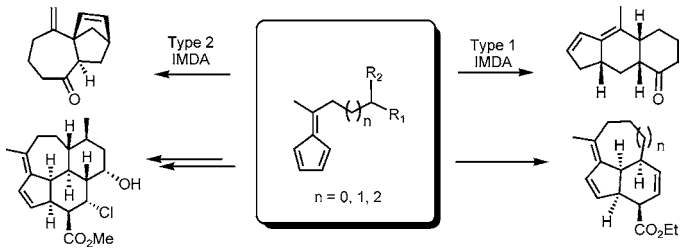
ABSTRACT



A variety of polycyclic ring skeletons (e.g., kigelinol, neoamphilectane, and kempene systems) can be prepared rapidly via intramolecular Diels–Alder cycloadditions (IMDA) of fulvenes. The length of the tethers and the diversity of the substituents on the fulvene core dictate the nature of the IMDA pathway.

Synthetic strategies for preparing appropriately functionalized polycyclic ring systems remain of major interest in organic chemistry. Among them, the intramolecular Diels−Alder reaction (IMDA) provides a powerful tool for the construction of complex carbocycles.[1] In conjunction with our continuing efforts in fulvene chemistry,[2] we embarked on a strategy that called for the construction of a variety of complex polycycles (e.g., the kigelinol and kempanes skeletons) from simple acyclic fulvene molecules. The idea stems from the well-established diversity-oriented synthetic (DOS) strategies,[3] with the exception that in this case, variation of the functional groups and tethers around a basic template, namely the fulvene core, followed by an IMDA cyclization would theoretically lead to diversity in the final products. Scheme 1 shows the retrosynthetic analysis of several naturally occurring carbocycles that may be prepared via the IMDA reaction of fulvenes. Kingelinol and isokigelinol were isolated from the root bark of *Kigelia pinnata* and show antitrypanosomal activity against *Trypanosoma brucei*.[4] Neoamphilectane, with its 5−6−6 tricyclic system, was

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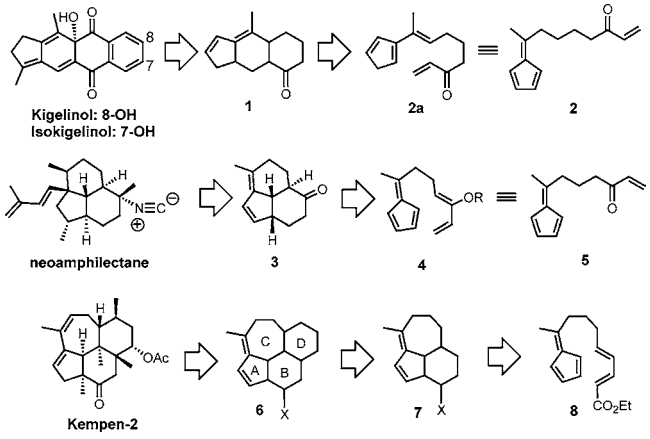
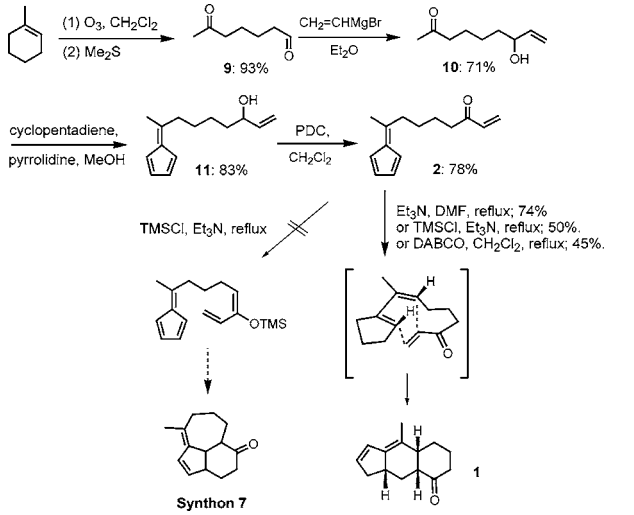
Scheme 1



Scheme 2



isolated from the tropical marine sponge *Cymbastela hooperi*, and shows potent antimalarial activity and cytotoxicity against *Plasmodium falciparum* clones and KB cells.[5] The cembrene-derived tetracyclic diterpenes (e.g., kempanes and rippertanes) were isolated from the secretions of nasute soldier termites.[6]

Dauben et al. reported a 23-step synthesis of kempene-2 that included a Diels−Alder cycloaddition and a Ti-induced McMurry cyclization of a keto aldehyde.[7] Paquette et al. described an approach to the kempane skeleton via an efficient palladium-catalyzed [3 + 2] cycloaddition,[8] and in 1993, Mertz et al. described an enantioselective approach to this system.[9] More recently, Burnell and co-workers reported a 19-step synthesis of the kempane ring system employing a Diels−Alder cycloaddition as the key transformation.[10] Examples of intermolecular Diels−Alder reactions of fulvenes are well-documented,[11] while examples of the corresponding IMDA are rare.[12] We envisioned that the key intermediate **1** for the synthesis of kigelinol could be prepared via an IMDA reaction of fulvene enone **2a**, which in turn is generated by isomerization of fulvene **2** during the reaction. Fulvene **2** was subsequently synthesized from methylcyclohexene in four steps and 43% total yield, Scheme 2.

Ozonolysis of methylcyclohexene (O_3, CH_2Cl_2; Me_2S, CH_2Cl_2; 93% yield), followed by slow addition of vinylmagnesium bromide to keto aldehyde **9** at 10 °C gave allyl alcohol **10** in 71% yield. Reaction of **10** with cyclopentadiene in the presence of pyrrolidine in MeOH provided fulvene **11** in 83% yield. Oxidation of **11** (Dess−Martin periodate or PDC in CH_2Cl_2, 78% yield) afforded enone **2** which reacted smoothly with Et_3N in refluxing DMF to provide the desired intermediate **1** in 74% yield. The single-crystal X-ray analysis of **1a** confirmed the structure and stereochemistry of **1**, Figure 1.[13] Surprisingly, treatment of **2** with TMSCl−Et_3N−DMAP in CH_2Cl_2 followed by an IMDA led to the formation of **1** (50% yield) instead of the desired synthon **7**. The same result was obtained when ketone **2** was reacted with DABCO in CH_2Cl_2. The regioselective *syn*-addition of the diene across one of the double bonds of cyclopentadiene on the fulvene provides the tricyclic 1*H*-cyclopenta[*b*]naphthalene, a motif which is found in numerous natural products and pharmaceutical agents, such as SP-18904,[14] treprostinil,[15] bisacutifolone,[16] pycnanthuquinone,[17] and kigelinol.

A similar approach was used in the four-step synthesis of fulvene enone **5** from methylcyclopentene (30% overall yield), Scheme 3. Unfortunately, heating enone **5** with Et_3N in DMF afforded the 2,4-[*a*]methanobenzocycloheptene **15** instead of the desired compound **4**.[18] The structure of **15** (a unique tricyclic core in artesieversin, plagiospirolide E, and biennin C) was confirmed by a single-crystal X-ray analysis

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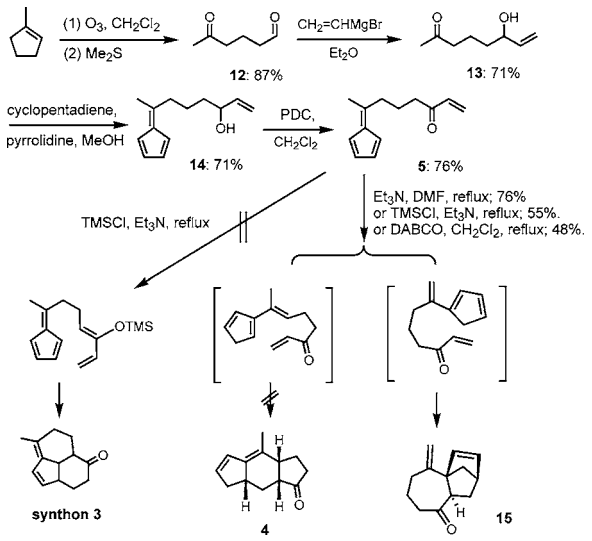
(13) **1a** was prepared from the reaction of **1** with 2,4-dinitrophenylhydrazine in EtOH. Crystallographic data for **1a**: $C_{20}H_{22}N_4O_4$, $M = 382.42$, monoclinic, space group $P2_1/c$, $T = 295(2)$ K, $a = 8.2559(5)$ Å, $b = 6.0132(4)$ Å, $c = 38.196(3)$ Å, $\beta = 93.358(2)°$, $V = 1893.0(2)$ Å^3, $Z = 4$, $D = 1.342$ g/cm^3, λ (Mo Kα) = 0.71073 Å, 15220 reflections collected, 4346 unique reflections, 255 parameters refined on F^2, $R = 0.0911$, $wR2[F^2] = 0.1978$ [2941 data with $F^2 > 2\sigma(F^2)$].

(14) An antihyperglycemic agent isolated from *Pycnanthus angolensis*, see: Luo, J.; Cheung, J.; Yevich, E. M.; Clark, J. P.; Tsai, J.; Lapresca, P.; Ubillas, R. P.; Fort, D. M.; Carlson, T. J.; Hector, R. F.; King, S. R. *J. Pharmacol. Exp. Ther.* **1999**, *288*, 529.

Scheme 3



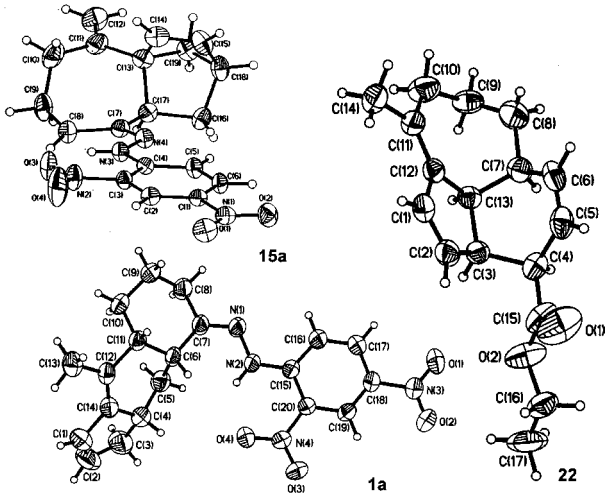


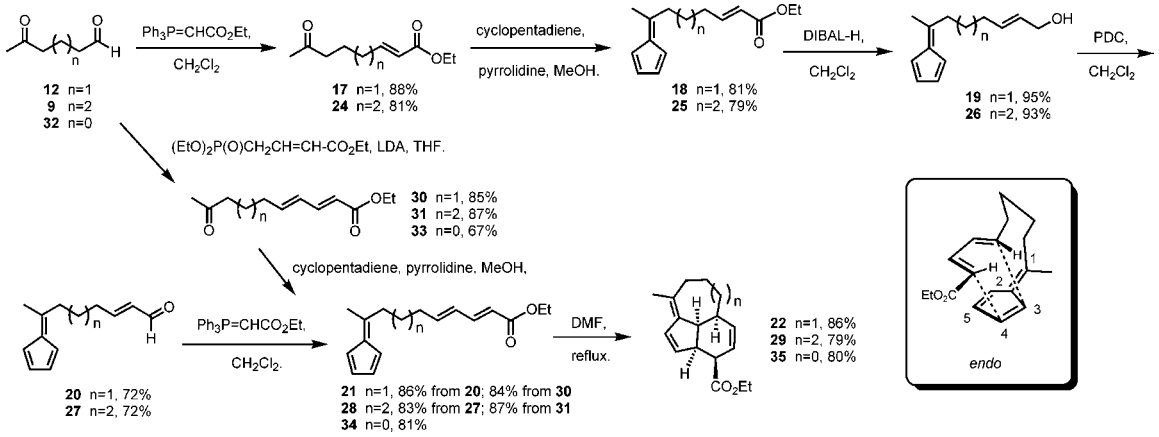
Figure 1. ORTEP plots for X-ray crystal structures of **1a**, **15a**, and **22**.

of its 2,4-DNP derivative (**15a**), Figure 1.[19] Attempts at preparation of **3** via the IMDA of silylated **5** also resulted in the formation of **15**. This may be a direct consequence of the shorter tether in **5** which results in a higher ring strain energy during the IMDA cyclic transition state.

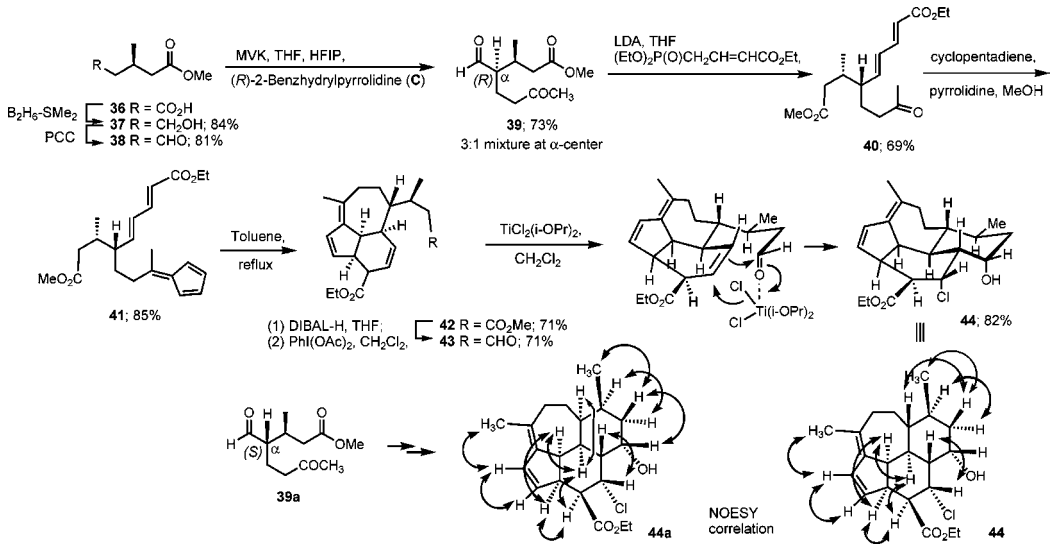
Compounds **6** and **7** were selected as key intermediates for the synthesis of the kempene system, and we believed that an IMDA of fulvene **21** could potentially lead to synthon **8**, Schemes 1 and 4. Based on previous observations in our group,[20] we opted to use an inverse-electron-demand Diels−Alder reaction in this case.[21] Hence, fulvene **21** was prepared from 5-oxohexanal (**12**) in 5 steps and 49% total yield, Scheme 4. Wittig reaction of **12** with $Ph_3P{=}CHCO_2Et$ in CH_2Cl_2 afforded ester **17** in 88% yield. Reaction of **17** with cyclopentadiene and pyrrolidine in methanol afforded fulvene **18**, which was reduced with DIBAL-H and oxidized with PDC to give aldehyde **20**. The Wadsworth−Emmons reaction of **20** provided fulvene **21** in 72% yield. Heating **21** in DMF afforded the desired benzo[*cd*]azulene **22** in 86% yield. The structure of **22** was confirmed by a single-crystal X-ray analysis, Figure 1.[22] The stereochemistry of the A−B−C tricyclic core of **22** was identical to that of the kempene systems. An efficient synthesis of **21** was also achieved in two steps from **12** via a Wadsworth−Emmons reaction with $(EtO)_2P(O)CH_2CH{=}CHCO_2Et$, followed by a standard fulvene formation reaction. Similarly, cycloocta[*cd*]indene **29** and acenaphthylene **35** (the tricycle skeleton of neoamphilectane, Scheme 1) were prepared from fulvenes **9** and **32**, respectively, Scheme 4.

Encouraged by these results, we embarked on an enantioselective synthesis of the kempene tetracyclic carbocycles, Scheme 5. Selective reduction of **36**[23] with $BH_3{-}SMe_2$, followed by oxidation with PCC gave **37** and **38** in 84% and 81% yield, respectively. Stereoselective Michael reaction of **38** and MVK with (*R*)-2-benzhydrylpyrrolidine gave **39** in 73% yield and 50% diastereomeric excess.[24] Wadsworth−Emmons reaction of **39** with triethyl-4-phosphonocrotonate afforded diene **40** in 69% yield, which was transformed into

Scheme 4



Scheme 5



fulvene **41** under standard conditions (cyclopentadiene, pyrrolidine, MeOH; 85% yield). Heating **41** in toluene provided tricyclic ester **42,** stereoselectively, in 71% yield. Aldehyde **43** was prepared in 71% yield by selective reduction of the methyl ester with DIBAL-H, followed by a Dess−Martin oxidation.[25] Prins reaction of **43** with $TiCl_2$-(*i*-OPr)$_2$ in CH_2Cl_2 gave the kempene tetracycle **44** (82% yield).[26] The proposed mechanism of the Prins reaction is depicted in Scheme 5. The stereochemistry of **44** was assigned on the basis of the ^{1}H, ^{13}C, HMQC, COSY, and NOESY spectra.[27]

In conclusion, we have described an efficient means to assemble the basic skeleton of kigelinol, neoamphilectane, and kempene using a novel diversity based intramolecular Diels−Alder cycloaddition of fulvenes. In addition, the tetracyclic core of kempene **44** was prepared in nine steps from commercially available methyl (*R*)-(+)-3-methylglutarate in 12% overall yield.

Acknowledgment. We are grateful to Dr. Sepehr Sarshar for valuable discussions. Financial support from the National Science Council is gratefully acknowledged.

Supporting Information Available: Crystallographic information files (CIF) for **1a**, **15a**, and **22**, along with experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) An epoprostenol analogue for primary pulmonary hypertension, see: McLaughlin, V. V.; Gaine, S. P.; Barst, R. J.; Oudiz, R. J.; Bourge, R. C.; Frost, A.; Robbins, I. M.; Tapson, V. F.; McGoon, M. D.; Badesch, D. B.; Sigman, J. *J. Cardiovas. Pharmacol.* **2003**, *41*, 293.

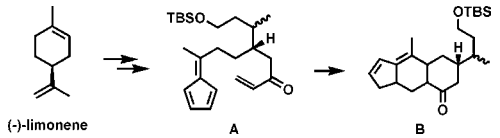
(16) Isolated from the Japanese liverwort *Porella acutifolia*, see: Hashimoto, T.; Irita, H.; Tanaka, M.; Takaoka, S.; Asakawa, Y. *Phytochemistry*, **2000**, *53*, 593.

(17) Isolated from the leaves and stems of the African plant *Pycnanthus angolensis*, see: Fort, D. M.; Ubillas, R. P.; Mendez, C. D.; Jolad, S. D.; Inman, W. D.; Carney,. R.; Chen, J. L.; Laniro, T. T.; Hasbun, C.; Bruening, R. C.; Luo, J. *J. Org. Chem.* **2000**, *65*, 6534.

(18) This may have occurred via a type-2 IMDA process of the fulvene. For a recent review, see: Bear, B. R.; Sparks, S. M.; Shea, K. J.; *Angew. Chem., Int. Ed.* **2001**, *40*, 820.

(19) Crystallographic data for **15a**: $C_{19}H_{19}N_4O_4$, M = 367.38, monoclinic, space group $P2_1/n$, T = 293(2) K, a = 9.7950(10) Å, b = 12.533(2) Å, c = 15.010(2) Å, β = 106.890(10)°, V = 1763.2(4) Å^3, Z = 4, D = 1.384 g/cm^3, λ (Mo $K\alpha$) = 0.71073 Å, 3912 reflections collected, 3077 unique reflections, 249 parameters refined on F^2, R = 0.0719, $wR2[F^2]$ = 0.1887 [1851 data with $F^2 > 2\sigma(F^2)$].

(20) Unpublished results: fulvene enone **A**, an analogue of **5**, was prepared from (−)-limonene, and the IMDA reaction gave tricycle **B**.

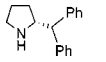


(21) Inverse-electron-demand Diels−Alder reactions usually afford a different periselectivity. For recent reviews, see: (a) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379. (b) Behforouz, M.; Ahmadian, M.; *Tetrahedron* **2000**, *56*, 5259. (c) Boger, D. L. *Chemtracts: Org. Chem.* **1996**, *9*, 149. For reaction with 1-azadiene, see: Mohammad B.; Mohammad A. *Tetrahedron* **2000**, *56*, 5259.

(22) Crystallographic data for **22**: $C_{17}H_{22}O_2$, M = 258.35, monoclinic, space group $P2_1/c$, T = 295(2)K, a = 11.6349(11) Å, b = 9.5265(8) Å, c = 14.2117(12) Å, β = 112.492(2)°, V = 1455.4(2) Å^3, Z = 4, D = 1.179 g/cm^3, λ (Mo $K\alpha$) = 0.71073 Å, 9246 reflections collected, 3340 unique reflections, 199 parameters refined on F^2, R = 0.0718, $wR2[F^2]$ = 0.1781 [2035 data with $F^2 > 2\sigma(F^2)$].

(23) Purchased from Fluka [63473-60-9].

(24) (a) For a recent enantioselective Michael addition of aldehydes to vinyl ketones catalyzed by (*S*)-pyrrolidine derivatives, see: Melchiorre, P.; Jørgensen, A. *J. Org. Chem.* **2003**, *68*, 4151. (b) Reaction of **38** with (*S*)-2-benzhydrylpyrrolidine gave a 4:1 mixture of the (*S*) isomer at the α center. (c) Reaction of **38** with Et_2NH gave a 1:1 mixture of the (*S*) and (*R*) isomers at the α center.



(*R*)-2-Benzhydryl-pyrrolidine (**C**)

(25) Various attempts at the selective DIBAL-H reduction the methyl ester to the aldehyde in the presence of the ethyl ester failed. Reaction in THF gave the best selectivity but afforded the alcohol instead.

(26) (a) The chloro-Prins reaction of hex-5-enal to 3-chloro-cyclohexanol system has been reported; see: Wölfling, J.; Frank, É.; Mernyák, E.; Bunkóczi, G.; Seijo, J. A. C.; Schneidera, G. *Tetrahedron* **2002**, *58*, 6851. (b) For a review of the Prins reaction, see: Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661. (c) For a recent review of the Pinacol-terminated Prins cyclization, see: Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143.

(27) The **44** and α-isomer of **44** (i.e., **44a**) were respectively prepared from **39** and **39a** (*S* isomer on the α center) and characterized; all spectral data are consistent with this structural assignment.