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Intramolecular Diels–Alder Reactions of Decatrienoates: Remote Stereocontrol and Conformational Activation[1]

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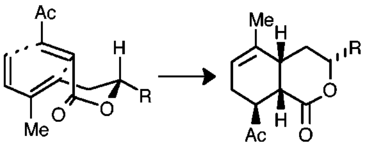
ABSTRACT



endo/boat
9; R = ^{t}Bu
[4a; R = H]

11

The intramolecular Diels–Alder (IMDA) reactions of C(8)-substituted decatrienoates have been studied. The stereospecific formation of 11 via an *endo*-boat-9 transition state attests to the powerful directing influence of a C(8) substituent in the IMDA of decatrienoate. In addition, the contrasting observations that stereospecific 9 → 11 occurs at room temperature while the nor-*tert*-butyl substrate (4a) requires 125 °C/5 h reaction conditions and produces a 60:40 mixture of diastereomers provide clear evidence that a bulky C(8) substituent is a powerful conformational activator of the IMDA.

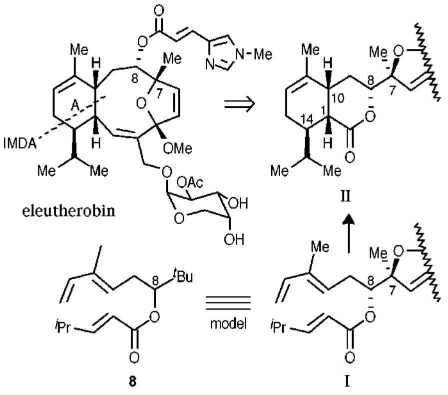


Figure 1. Considerations for eleutherobin “A-ring” construction.

In the course of studies directed toward total syntheses of eleuthesides (e.g., eleutherobin, sarcodictyins), we have undertaken a study of the intramolecular Diels−Alder reaction (IMDA)[2] of decatrienoate systems (Figure 1). While both the Nicolaou[3] and Danishefsky[4] groups have reported total syntheses of eleutherobin, their strategies proceeded by elaboration of A-ring precursors (+)-carvone and (−)-phellandrene, respectively. Our objective was to develop eleutheside synthetic strategies that readily accommodate A-ring modification. We selected an IMDA route because in-depth analysis of the competing cycloaddition transition

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[1] (a) Presented at the 219th National Meeting of the American Chemical Society, San Francisco, CA, March 26−30, 2000; ORGN 343. (b) For a related study, see: Jung, M. E.; Huang, A.; Johnson, T. W. *Org. Lett.* **2000**, *2*, 1835−1837.

[2] (a) Alder, K.; Schumacher, M. *Fortsch. Chem. Org. Naturst.* **1953**, *10*, 66. (b) Roush, W. R. In *Comprehensive Organic Synthesis*, Vol. 5; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; pp 513−550. (c) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187−238. (d) Taber, D. F. *Intramolecular Diels−Alder and Alder Ene Reactions*; Springer: Berlin, 1984. (e) Ciganek, E. *Org. React.* **1984**, *32*, 1−374.

[3] (a) Hamel, E.; Sackett, D. L.; Vourloumis, D.; Nicolaou, K. C. *Biochemistry* **1999**, *38*, 5490−8. (b) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Pfefferkorn, J.; Ohshima, T.; Vourloumis, D.; Hosokawa, S. *J. Am. Chem. Soc.* **1998**, *120*, 8661−73. (c) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2520−4. (d) Nicolaou, K. C.; Xu, J. Y.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353−4.

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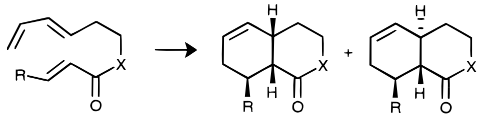
states available to decatrienoates such as **I** suggested that the IMDA reaction would deliver the requisite C(10)/C(1)/C(14) stereochemistry as a function of C(8) stereochemistry. Herein we report the details of this study.

The Literature Perspective. The intramolecular Diels–Alder reactions of substituted *decatrienones* have been well studied,[5] and representative examples[6] are shown in Table 1. From these examples, it can be seen that *exo* addition of a *trans*-oriented side chain [e.g., an (*E*)-diene] leads to a *trans*-fused ring system while *endo* addition of a *trans*-tethered dienophile leads to a *cis*-fused ring system. From Table 1, we note that the reactions of decatrienones proceed with excellent *endo* addition selectivity. Extensive decatrienone cycloaddition studies[7] also confirm a strong preference for *endo* addition.

Table 1. Controlling Bridgehead Stereochemistry



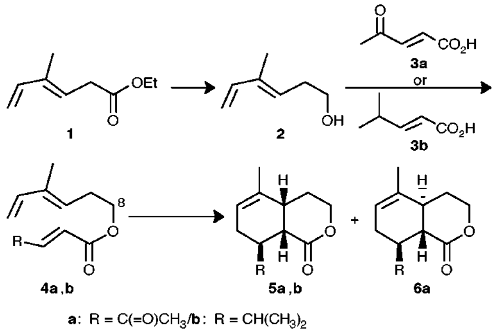
entry	cis	trans	ref
a: X = CH_2, R = H	95	5	5
b: X = CH_2, R = ^{i}Pr	100	0	5
c: X = O, R = H	90	10	6
d: X = NMe, R = H	88	12	6

Observations on the cycloaddition reactions of several decatrienone systems led Roush to observe[7] that “in the absence of overriding nonbonded or electronic interactions the *cis*-fused, boat-like decatrienone transition state should be favored over the more usually invoked chair-like arrangement.” Decatrienone studies by Zschiesche et al. suggest that **8** will react via an *endo*-boat transition state instead of an *endo*-chair arrangement.[8]

A C(8) Anchor Role? With these observatoins in hand, analysis of the four *endo*-transition states available to **8** suggested to us a “face-selecting” role of the C(8) substituent. Relative to C(8), there are two *endo* additions possible for each face of the diene. In one of these *endo* transition states, the C(8) *tert*-butyl group resides in an axial position on the cyclohexane chair and is highly destabilized. In another *endo* transition state, the C(8) *tert*-butyl group resides in a pseudoaxial position on a cyclohexane boat-like transition state and is also highly destabilized. The remaining two *endo* transition states place the C(8) *tert*-butyl group in equatorial positions, and reaction via these transition states is expected to be highly favored. The implication in this analysis is that **I** must have the (*R*)-configuration at C(8) to direct the formation of correct eleutherobin configurations at C(10), C(1), and C(14).

Calibration Studies—No C(8) Anchor (Scheme 1). Reduction of unconjugated ester **1**[9] with diisobutylaluminum hydride gave dienol **2**[10] in 91% yield (Scheme 1). Decatrienoates **4a** and **4b** were then prepared in moderate yield from this dienol and *trans*-α,*β*-unsaturated acids **3a**[11] and **3b**[12] using DCC and DMAP (**4a** = 80%; **4b** = 73%).[13] Initial cycloadditions with these two substrates were performed using toluene-d_8 in sealed NMR tubes to establish appropriate reaction conditions.

Scheme 1. Calibration Studies—No C(8) Anchor



For bis-activated **4a**, cycloaddition was effected by heating a sealed-vessel toluene solution at 125 °C for 5 h, yielding two isomeric products in 52% combined yield (**5a**:**6a** 60:40). Chromatographic purification yielded the minor isomer (**6a**) as a white crystalline solid, while the major isomer (**5a**) was obtained as a colorless oil. Single-crystal X-ray analysis established that **6a** is a *trans*-fused bicyclic product arising from a boat transition state with the ester moiety occupying an *exo* position. COSY and proton decoupling NMR experiments on the major isomer (**5a**) established the coupling constant between the two bridgehead protons as 7.5 Hz, clearly indicating that **5a** has a *cis* ring fusion. Cycloadducts **5a** and **6a** do not equilibrate under these reaction conditions.

For monoactivated **4b**, cycloaddition required heating a sealed-vessel toluene solution at 220 °C for 20 h. Only one cycloadduct (**5b**) was obtained from this reaction, and proton decoupling NMR experiments established that it was a *cis*-

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(4) The Danishefsky group has also reported the total synthesis of eleutherobin: (a) Chen, X. T.; Bhattacharya, S. K.; Zhou, B. S.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563–79. (b) McDaid, H. M.; Bhattacharya, S. K.; Chen, X. T.; He, L. F.; Shen, H. J.; Gutteridge, C. E.; Horwitz, S. B.; Danishefsky, S. J. *Cancer Chemother. Pharmacol.* **1999**, *44*, 131–7. (c) Chen, X. T.; Zhou, B. S.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 789–92.

(5) Reviews: (a) Fallis, A. G. *Can. J. Chem.* **1984**, *62*, 183–234. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63–97.

(6) (a) Oppolzer, W.; Snowden, R. L.; Simmons, D. P. *Helv. Chim. Acta* **1981**, *64*, 2002–21. (b) Gras, J. L. *J. Org. Chem.* **1981**, *46*, 3738–41. (c) See page 201 of ref 5a. (d) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170–80.

(7) Roush, W. R. In *Advances in Cycloaddition*, Vol. 2; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1990; pp 91–146.

(8) Zschiesche, R.; Frey, B.; Grimm, E.; Reissig, H.-U. *Chem. Ber.* **1990**, *123*, 363–374.

(9) Shing, T. K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 2187–94.

(10) Chwang, W. K.; Knittel, P.; Koshy, K. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1977**, *99*, 3395–401.

(11) Porter, N. A.; Scott, D. M.; Rosenstein, I. J.; Giese, B.; Veit, A.; Zeitz, H. G. *J. Am. Chem. Soc.* **1991**, *113*, 1791–9.

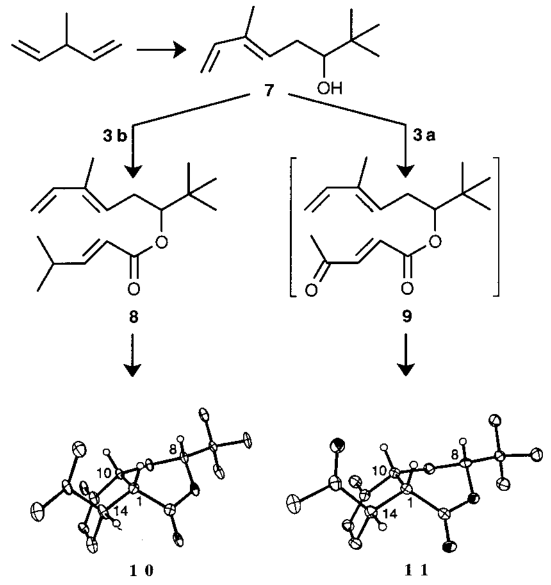
(12) Pirrung, M. C.; Han, H.; Ludwig, R. T. *J. Org. Chem.* **1994**, *59*, 2430–6.

(13) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475–8.

fused product (coupling constant between the two bridgehead protons = 6.6 Hz). Chromatographic purification gave **5b**, the product arising from a boat transition state with the ester group adding *endo*, as a colorless oil in 43% yield from **4b**.

C(8) Anchor Effects (Scheme 2). We selected dienol **7**[14] as the best substrate for evaluating the role of a C(8) substituent in decatrienoate Diels−Alder reactions. Dienol **7** was prepared in 90% yield by lithiation of 3-methyl-1,4-pentadiene (^{n}BuLi, THF) and subsequent addition of trimethylacetaldehyde.

Scheme 2. C(8) Anchor Effects



Esterification of **7** with *trans*-4-methyl-2-pentenoic acid (**3b**; DCC, DMAP) delivered decatrienoate **8** in 87% yield. The IMDA reaction was accomplished by heating a sealed vessel solution of **8** in toluene at 200 °C for 12 h. A single product (**10**) was obtained in 55% yield, and single-crystal X-ray analysis of this solid (colorless tetragonal needles from EtOAc/hexanes) estabilshed the stereochemistry to be as shown in Scheme 2.

In the case of Diels−Alder precursor **9**, esterification with *trans*-4-oxo-2-pentenoic acid (**3a**; DCC, DMAP) delivered the transient decatrienoate which, without isolation,[15] underwent IMDA cycloaddition giving **11** as the sole product (colorless triclinic block from EtOAc/hexanes) in 91% yield. The structure of cycloadduct **11** was also confirmed by X-ray crystallography (see Scheme 2).

The C(8) Anchor—A Powerful IMDA Control Element. Viewed in concert, the IMDA results obtained with decatrienoates **4a**, **4b**, **8**, and **9** provide clear evidence of the *endo* and *boat* directing effects of a C(8) substituent. Beginning with **10**, the model compound directly related to eleutherobin, the *endo*-chair-**8** transition state (Figure 2), can be ruled out and the *syn*/*cis*/*anti* [C(8)H−C(10)H/C(10)H−C(1)H/C(1)H−C(14)H, respectively] stereochemistry of **10** can be explicitly viewed as arising via an *endo*-boat-**8** Diels−Alder transition state. Just as clearly, *syn*/*cis*/*anti*-**11** cannot arise from *endo*-chair-**9** and must arise via *endo*-boat-**9**. The fact that we observe no trace of the *syn*/*trans*/*anti*-isomer of **11**[16] indicates that *endo*-boat-**9** is much preferred over *exo*-chair-**9**. The *cis*/*anti* [C(10)H−C(1)H/C(1)H−C(14)H, respectively] stereochemistry of **5b** is consistent with either an *endo*-boat or an *endo*-chair cycloaddition transition state of **4b**. However, to the extent that *endo*-chair-**4b** mirrors unfavorable *exo*-chair-**9**, **5b** probably arises via *endo*-boat-**4b**. Similar observations apply to the formation of **5a** and **6a** via *endo*-boat-**4a** and *exo*-boat-**4a**, respectively.

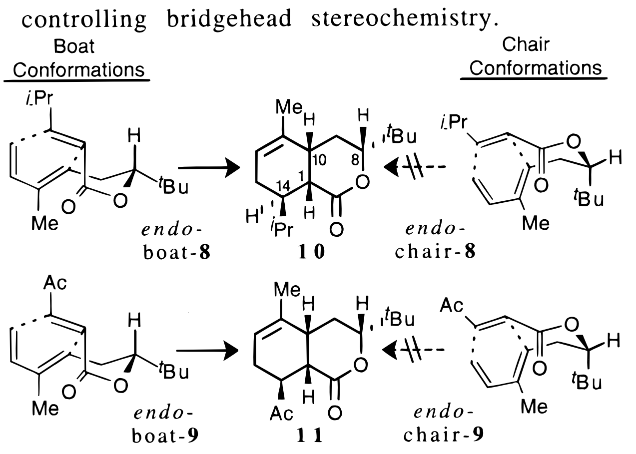


Figure 2. Controlling bridgehead stereochemistry.

The contrasting selectivities of **9** leading only to **11** versus **4a** leading to both **5a** and **6a** (60:40, respectively) attest to the powerful directing influence of a C(8) substituent in the IMDA of decatrienoates. In addition, the 125 °C/5 h reaction conditions required for **4a** → **5a**/**6a** versus the facile room temperature/12 h required for **9** → **11** (this IMDA occurs as **9** is formed from **7** over a 12 h period) provide clear evidence that a C(8) substituent is a powerful IMDA activator. This activation effect is the consequence of strong decatrienoate conformational biasing. This study strengthens the predictive power for unambiguous application of the IMDA reaction of decatrienoates. We are encouraged that a decatrienoate such as **I** (Figure 1) will deliver intermediate **II** via a highly selective *endo*-boat-**I** transition state. These studies are underway and will be reported in due course.

Acknowledgment. We are grateful to the National Science Foundation for financial support of this research.

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(14) (a) Plietker, B. Ph.D. Thesis, Technische Universität Dresden, 1999, pp 124−126. (b) Metz, P.; Fleischer, M.; Fröhlich, R. *Tetrahedron* **1995**, *51*, 711−32.

(15) For an analogous example of spontaneous cycloaddition of a C('7')-substituted decatrienone, see: Taber, D. F.; Gunn, B. P. *J. Am. Chem. Soc.* **1979**, *101*, 3992−3.

(16) Compound **i**; see Supporting Information for a complete comformational anaylsis figure.

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Supporting Information Available: Experimental data for all compounds and a comformational anaylsis figure. This material is available free of charge via the Internet at http://pubs.acs.org.

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