ORGANIC LETTERS

2011
Vol. 13, No. 12
3274–3277

Complete Facial Selectivity in the Diels–Alder Reaction of a 5-Amino-5-carboxycyclopentadiene Derivative

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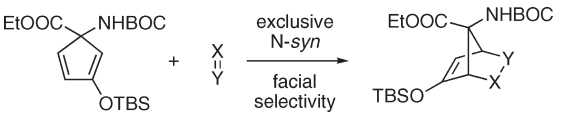
Received May 10, 2011

ABSTRACT



5-*tert*-Butoxycarbonylamino-5-carbethoxy-2-*tert*-butyldimethylsilyloxy-cyclopentadiene undergoes a Diels–Alder reaction exclusively from the face *syn* to the nitrogen functionality. Complete reversal of facial bias may be achieved, but at the cost of diminished reactivity, through steric shielding of the N-*syn* face.

Synthetic efforts underway in our group have unveiled the desirability of a facially selective Diels–Alder reaction of a cyclopentadiene such as **1** (Figure 1). Compounds of this type are special cases of siloxy dienes[1] but were undocumented at the onset of our investigations. Indeed, most known 5-substituted cyclopentadienes carry a single substituent at that position.[2] If this substituent is an alkyl group, then the diene tends to engage dienophiles from the face opposite the C-5 substituent, i.e., with C-5 alkyl-*anti* facial bias: a preference attributed to steric effects. Known monosubstituted cyclopentadienes carrying a heteroatomic group at C-5 differ from **1** in that they lack the activating siloxy unit, and none incorporate nitrogen at C-5. The facial selectivity of the Diels–Alder reactions of such dienes is sensitive to subtle structural differences.

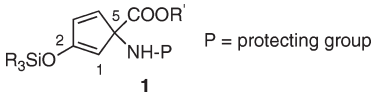


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Figure 1. Cyclopentadienes of interest in this study.

Namely, **4a**[3] and **4c**[4] display complete halogen-*syn* faciality, but for reasons that remain unclear, **4b** reacts with a modest 2:1 = Cl-*syn* bias (Table 1).[4] Considerably less literature exists on the behavior of 5,5-disubstituted cyclopentadienes, perhaps because these species tend to react with poor facial selectivity. Thus, the Diels–Alder reaction of **5**[5] and **6a**[6] occurs with no facial bias, while **6b** exhibits weak R-*anti* preference.[7] However, diene **7a**[8] exhibits moderate COOEt-*syn* faciality (5: 1), a preference that is greatly enhanced in **7b** (complete *N-syn* selectivity).[9] If

(1) Reviews: (a) Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400. (b) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (c) Danishefsky, S.; Kitahara, T.; Schuda, P. F. *Org. Synth., Coll. Vol. VII* 1990, 312.

(2) Representative siloxy cyclopentadienes and their chemistry: (a) Snowden, R. L. *Tetrahedron Lett.* **1981**, *22*, 97. (b) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. (c) Kodpinid, M.; Siwapinyoyos, T.; Thebtaranonth, Y. *J. Am. Chem. Soc.* **1984**, *106*, 4862. (d) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1988**, *110*, 5911. (e) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3497. (f) Corey, E. J.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1996**, *118*, 11982. (g) Lalic, G.; Petrowski, Z.; Galonic, D.; Matovic, R.; Saicic, R. N. *Tetrahedron* **2001**, *57*, 583. (h) Ashenhurst, J. A.; Gleason, J. L. *Tetrahedron Lett.* **2008**, *49*, 504. (i) Hudon, J.; Cernak, T. A.; Ashenhurst, J. A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 8885. (j) Ashenhurst, J. A.; Isakovic, L.; Gleason, J. L. *Tetrahedron* **2010**, *66*, 368.

(3) McClinton, M. A.; Sik, V. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1891.

(4) Franck-Neumann, M.; Sedrati, M. *Tetrahedron Lett.* **1983**, *24*, 1391.

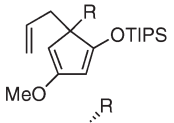
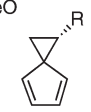
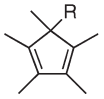
(5) Schulé, A.; Liang, H.; Vors, J.-P.; Ciufolini, M. A. *J. Org. Chem.* **2009**, *74*, 1587.

(6) (a) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793. Compound **6a** is a variant of the Corey cyclopentadiene:(b) Corey, E. J.; Shiner, C. S.; Volante, R. P.; Cyr, C. R. *Tetrahedron Lett.* **1975**, *16*, 1161.

(7) Reynaud, C.; Giorgi, M.; Doucet, H.; Santelli, M. *Synthesis* **2011**, 674.

10.1021/ol201236j
Published on Web 05/26/2011

Table 1. Facial Selectivity in the Diels–Alder Reaction of Some Cyclopentadienes Known Prior to the Present Study

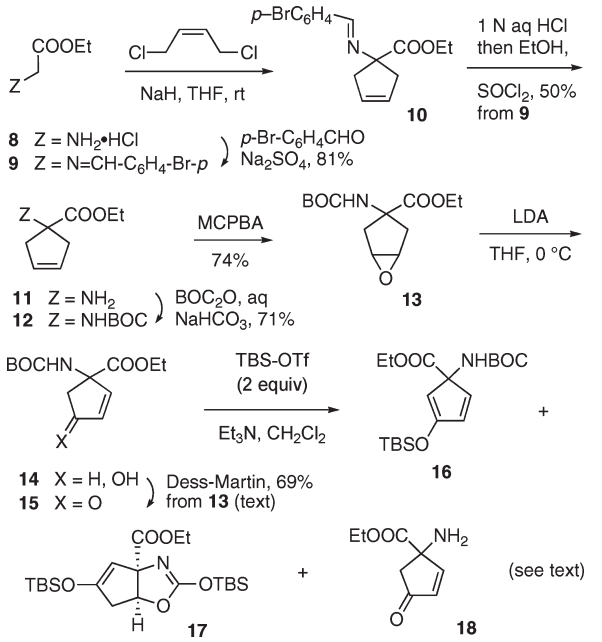
diene type	entry	R	facial select. [R-*syn*:R-*anti*]	reference
	**4a**	F	1:0	3
	4b	Cl	2:1	4
	4c	Br	1:0	4
	**5**	COOEt	1:1	5
	**6a**	CH_2OTBS	1:1	6
	6b	CH_2OH	1:2	7
	**7a**	COOEt	5:1	8
	7b	NH_2	1:0	9

C=O and N groups are both *syn*-directing, the simultaneous presence of such functionalities at the C-5 position of **1** made it unclear whether this diene would exhibit facial selectivity, and in which sense. Experimentation was needed to address this issue.

A suitable diene was made by enol silylation of enone **15** (Scheme 1). Enantioselective routes to **15** are known,[10,11] but optically enriched substrates were irrelevant to the objective of the present study, which aimed to address the question of facial selectivity. All work was thus conducted with racemic materials. The synthesis of (±)-**15**[10–12] started with alkylation of imine **9** with *cis*-1,4-dichloro-2-butene.

Subsequent imine cleavage (aq 1 N HCl) resulted in partial hydrolysis of the ester, necessitating subjection of the crude product to Fisher esterification to effect complete conversion into **11**. BOC-protection of the amine generated **12**, which reacted with MCPBA to afford a 5:1 (^{1}H NMR) mixture of unassigned diastereomers of epoxide **13**.[13] Smooth rearrangement to allylic alcohols **14** occurred

Scheme 1. Preparation and Enol Silylation of Enone **15**



upon reaction of the epoxide mixture with LDA. An ensuing Dess–Martin oxidation furnished **15** in 69% yield over two steps on a scale of 0.5 mmol.[14] The conversion of enone **15** into diene **16** was best carried out by reaction with TBSOTf and base.[15] However, the desired **16** was accompanied by variable quantities of byproducts **17** and **18**. The genesis of **17** is attributable to a Michael-type cyclization of the carbamate into the enone and concomitant exchange of the *tert*-butyl with a silyl group. The use of 1.5 equiv or less of TBS-OTf resulted in formation of a 1:1:1 mixture of **16**, **17**, and **18**. Reaction of **15** with 2 equiv of TBS-OTf and 2,6-lutidine generated only **18**, while replacement of lutidine with Hunig's base afforded only the bicyclic product **17**. Optimal results were obtained by treatment of **15** with 2 equiv of TBSOTf in the presence of Et_3N, whereupon a 1–1.2:1 mixture of **16** and **17** was obtained in 81% yield after chromatography on neutral alumina.[16] Unacceptable losses occurred upon attempted separation of the two components. Subsequent Diels–Alder experiments thus employed the mixture of **16** and **17**, since only the former can undergo cycloaddition. Diene **16** underwent a Diels–Alder reaction with maleic anhydride at room temperature

(8) (a) Ishida, M.; Tomohiro, S.; Shimizu, M.; Inagaki, S. *Chem. Lett.* **1995**, *24*, 739. (b) Ishida, M.; Hirasawa, S.; Inagaki, S. *Tetrahedron Lett.* **2003**, *44*, 2187. These authors also report that Diels–Alder reactions of an analogue of **7a** wherein a CN group replaces the COOEt unit proceed with complete CN-*syn* facial selectivity.

(9) Macaulay, J. B.; Fallis, A. G. *J. Am. Chem. Soc.* **1990**, *112*, 1136.

(10) Hodgson, D. M.; Thompson, A. J.; Wadman, S.; Keats, C. J. *Tetrahedron* **1999**, *55*, 10815.

(11) Varie, D. L.; Beck, C.; Borders, S. K.; Brady, M. D.; Cronin, J. S.; Ditsworth, T. K.; Hay, D. A.; Hoard, D. W.; Hoying, R. C.; Linder, R. J.; Miller, R. D.; Moher, E. D.; Remacle, J. R.; Rieck, J. A.; Anderson, D. D.; Dodson, P. N.; Forst, M. B.; Pierson, D. A.; Turpin, J. A. *Org. Process Res. Dev.* **2007**, *11*, 546.

(12) (a) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 113. (b) Park, K.-H.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 6579.

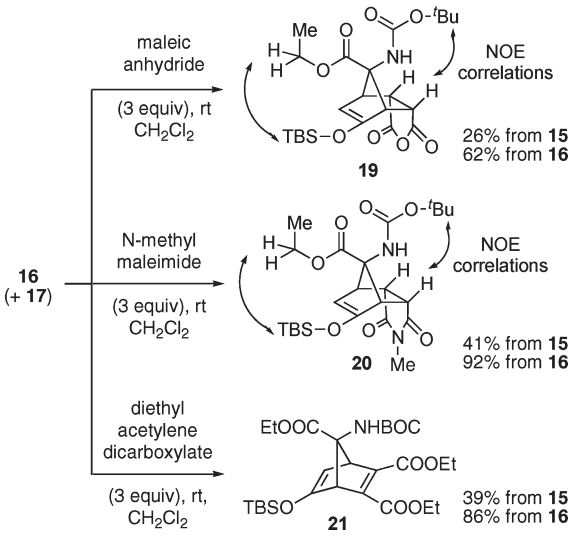
(13) The major isomer was obtained in pure form upon chromatography; however, no stereochemical characterization was carried out at this stage. The work Hodgson (ref 10) suggests that the major epoxide is likely to have the *syn* relationship between oxiranyl and nitrogen functions.

(14) The rearrangement step did not scale up well: the yield dropped to 27% when the same reaction was run with 6.5 mmol of epoxide. This is consistent with the results of Varie (ref 11). In the interest of time, the optimization of large-scale reaction conditions was postponed to a more favorable juncture.

(15) The formation of **16** by deprotonation (LDA) and silylation (TBS-Cl) proceeded cleanly, but in lower yield. Furthermore, our choice of a TBS enol ether was motivated by results obtained with other dienes related to **5** (ref 5). Briefly, a TBS group provides an ideal balance between chemical stability and reactivity. Moreover, the action of TESOTf and TIPSOTf on **15** afforded virtually only the cyclic product **17** and none of the desired **16**.

(16) Contact with silica induced considerable desilylation of the sensitive diene.

Scheme 2. Facially Selective Diels–Alder Reactions of Diene **16**



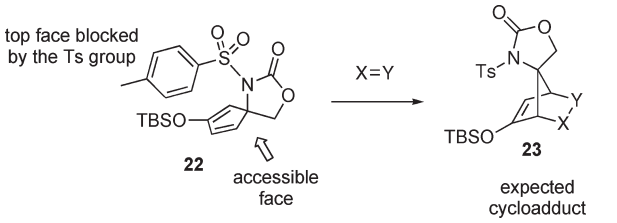
to yield cycloadduct **19** as a single diastereomer[17] (Scheme 2). The yield of purified (silica gel chromatography) **19** from **15** was 26% (62% from **16** as determined by ^{1}H NMR). The detection of strong dipolar coupling (2D-NOESY NMR) between the BOC group hydrogens and the *exo* H's, as well as between the ethyl ester methylene H's and the TBS group hydrogens, implied that the reaction had occurred in an *endo* mode and with complete *N-syn* facial selectivity.[17] The moderate yield of **19** proved to be a consequence of the sensitivity of the anhydride unit to silica gel.[18] Indeed, the product obtained from the reaction of **16** with *N*-methylmaleimide, also formed as a single diastereomer,[17] was considerably more stable than **19**, and it was isolated in 41% yield from **15** (92% from the 1:1 mixture of **16** and **17** as calculated by ^{1}H NMR). Again, the structure of **20** was assigned on the basis of NOESY spectroscopy, which confirmed that the product had originated from an *N-syn* facially selective *endo*-cycloaddition. The reaction of **16** with diethyl acetylenedicarboxylate also afforded a single diastereomer of the adduct[17] (39% yield from **15** after silica gel chromatography; 86% from the mixture of **16** and **17** by ^{1}H NMR). While an unequivocal stereochemical elucidation was not carried out, it seems unlikely that the new dienophile should have reacted with a faciality opposite that of the others. Therefore, we presume that the product of this reaction was **21**: the resultant of an *N-syn* selective cycloaddition.

Having determined that **16** exhibits *N-syn* facial bias, we sought to reverse such a preference. This could be done by increasing the steric demand of the nitrogen functionality while decreasing that of the ester group. Diene **22** (Scheme 3), wherein the arylsulfonyl residue bars approach of the dienophile from the *N-syn* face of the molecule, while the

(17) Within the limits of 300 MHz ^{1}H NMR spectroscopy.

(18) Chromatography on supports such as alumina or florisil afforded unacceptable levels of purification.

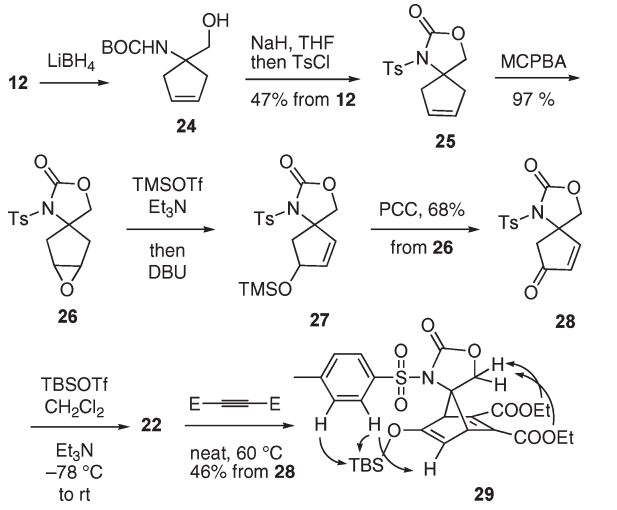
Scheme 3. Anticipated Facial Selectivity in the Diels–Alder Reaction of Diene **22**



N-anti face is readily accessible, seemed a good substrate for an *N-anti* facially selective Diels–Alder reaction.

The preparation of **22** commenced with $LiBH_4$ reduction of **12**, cyclization (NaH) of the resulting alcohol **24**, and *in situ* *N*-tosylation of the transient oxazolidinone anion (Scheme 4). Compound **25** emerged in 47% isolated yield over two steps.[19] Epoxidation produced **26** as a single diastereomer.[17] We presume, on steric grounds, that the epoxide was formed *anti* to the nitrogen functionality; however, the configuration of **26** was not ascertained. Contrary to the case of **13**, the rearrangement of **26** to an allylic alcohol was best carried out under Noyori conditions.[20] The resultant **27** was directly exposed to the action of PCC, the acidic nature of which induced both cleavage of the TMS ether and oxidation of the liberated alcohol[21] to afford **28** in 68% yield from **26**.

Scheme 4. Preparation of Diene **22** and Facially Selective Diels–Alder Reaction Thereof



(19) The yield of **28** was substantially higher when cyclization and tosyl protection were carried out in one pot, rather than as two distinct steps (47% vs 25%).

(20) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1979**, *101*, 2738.

(21) Muzart, J. *Synthesis* **1993**, 11.

(22) Enone **28** is only slightly soluble in organic solvents suitable for the conduct of this step (CH_2Cl_2, THF, ether, EtOAc), which therefore was carried out in dilute solution (*ca.* 0.02 M; some of **28** remained in suspension even after sonication). Importantly, diene **22** required no purification before use.

The subsequent enol silylation of **26** proceeded uneventfully,[22] but diene **22** displayed poor Diels–Alder reactivity, failing to combine even with freshly sublimed maleic anhydride.[23] Fortunately, acetylenedicarboxylic ester did react with **22** (60 °C, neat)[24] to give adduct **29** as a single diastereomer[17] (46% yield). Extensive NOESY-2D NMR experiments confirmed **29** to be the product of an *N-anti* facially selective Diels–Alder reaction.

All the results presented herein are consistent with a Cieplak-type[25] rationale.[26] A C-5 σ_{C-R} bond (R = alkyl or H) provides more efficient electron donation into the incipient σ^* orbitals associated with developing σ_{C-C} bonds relative to a C-5 σ_{C-Z} bond (Z = COOMe, NH_2, halogen; Figure 2). This translates into a more efficient stabilization of the transition state for a *Z-syn* Diels–Alder reaction and preferential formation of products arising from such a topology with dienes **4** and **7**. The lower electronegativity of C relative to N makes a C–C bond a more efficient electron donor than a C–N bond. Diene **16** thus favors reaction through transition state **30**, leading to products of *N-syn* facially selective cycloaddition. Finally, steric effects force diene **22** to react with *N-anti* faciality, a mode of reactivity that is disfavored on Cieplak grounds. Moreover, as the reaction proceeds, a decrease in the dihedral angle between N–C5–C1–C2 and N–C5–C4–C3 engenders compression of the Ts group against the remainder of the cyclopentadiene ring. Transition state **32** is thus destabilized both on electronic and on steric grounds, resulting in a slow overall rate. While it is indeed possible to override the inherent stereoelectronic preferences of the diene through sterics, the price for *N-anti* selectivity is a diminished reaction rate. Knowledge of the inherent facial bias of the dienes described herein is essential to the progress of research currently underway in our laboratory, and it could be of value in charting the synthesis of diverse nitrogenous substances.

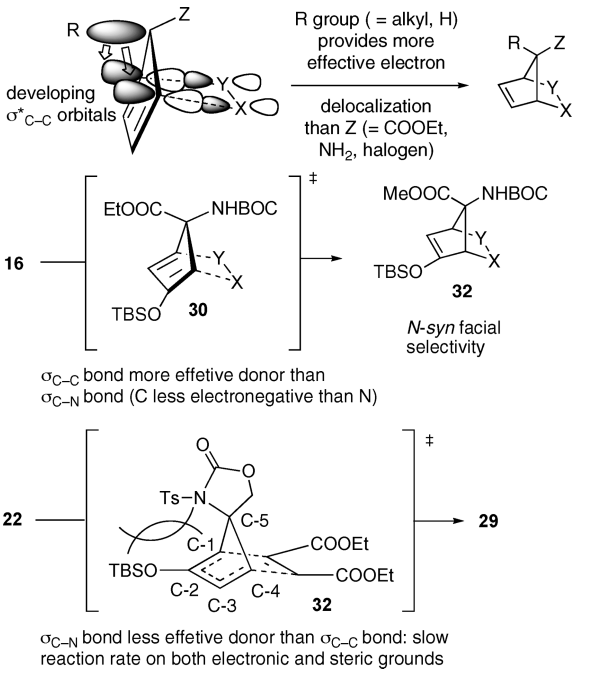


Figure 2. A Cieplak rationale for the observed results.

Acknowledgment. We thank the University of British Columbia, the Canada Research Chair Program, BCKDF, CFI, NSERC, and CIHR for financial support.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra (^1H and ^{13}C) of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(23) Only silyl group release occurred during several such attempts, regardless of temperature (rt to 60 °C), solvent (CH_2Cl_2 or benzene), nature of the silyl ether (TMS, TES, TIPS), or whether a Lewis acid (Me_2AlCl) was utilized to promote the Diels–Alder reaction, or a mild base (K_2CO_3; destruction of adventitious acid) was introduced to preserve the diene.

(24) No significant reaction occurred at room temperature (^1H NMR).

(25) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265.

(26) Review: (a) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278. We note that despite the successful predictions that arise from a Cieplak analysis, controversy exists in the literature concerning the origin of facial selectivity in such Diels–Alder reactions: (b) Anh, N. T. *Tetrahedron* **1973**, *29*, 3227. (c) Coxon, J. M.; McDonald, D. Q. *Tetrahedron Lett.* **1992**, *33*, 651. (d) Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4054. (e) Ishida, M.; Aoyama, T.; Beniya, Y.; Yamabe, S.; Kato, S.; Inagaki, S. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3430. (f) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980. (g) Kiri, S.; Odo, Y.; Omar, H. I.; Shimo, T.; Somekawa, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1499. (h) Kolakowski, R. V.; Williams, L. J. *Nat. Chem.* **2010**, *2*, 303. (i) Poirier, R. A.; Pye, C. C.; Xidos, J. D.; Burnell, D. J. *J. Org. Chem.* **1995**, *60*, 2328. (j) Pye, C. C.; Xidos, J. D.; Burnell, D. J.; Poirier, R. A. *Can. J. Chem.* **2003**, *81*, 14. (k) Xidos, J. D.; Poirier, R. A.; Pye, C. C.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 105. See also refs 8 and 9.