termination of the enantiomeric excesses and absolute configurations of the products (7 pages). Ordering information is given on any current masthead page.

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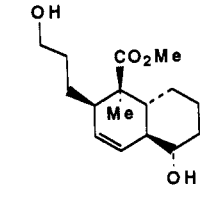
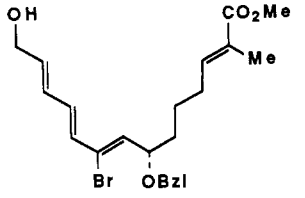
Enantioselective Synthesis of the Bottom Half of Chlorothricolide. 2. A Comparative Study of Substituent Effects on the Stereoselectivity of the Key Intramolecular Diels-Alder Reaction

Summary: The intramolecular Diels-Alder reactions of trienes **4-7** were studied to evaluate the ability of diene (TMS, Br) and dienophile (CHO, CO_2Me) substituents to influence Diels-Alder stereoselectivity and thereby define the optimal precursor to the bottom half of chlorothricolide.

Sir: In continuation of efforts to complete an enantioselective total synthesis of chlorothricolide, it became apparent that an improved synthesis of the bottom-half fragment **1** was required.[1] The key step of our previously



1



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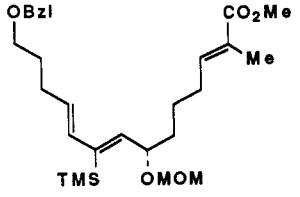

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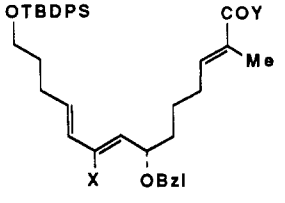


4, X = TMS, Y = OMe
5, X = Br, Y = OMe
6, X = TMS, Y = H
7, X = Br, Y = H

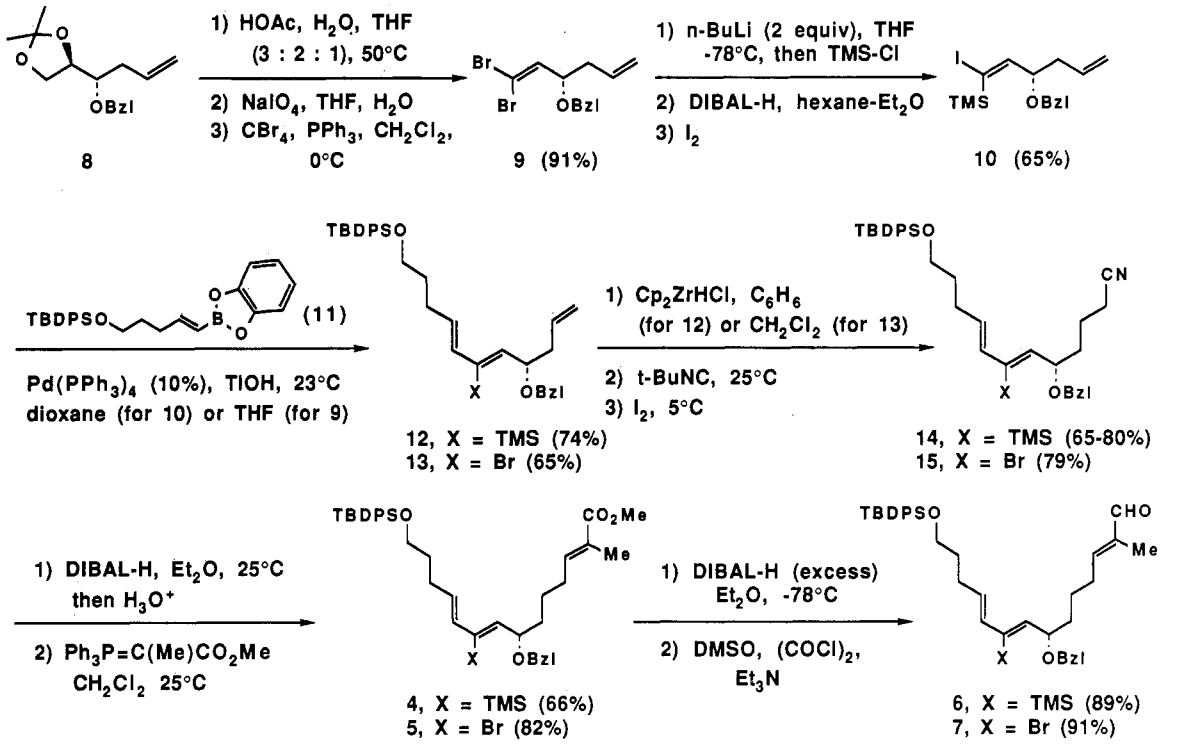
reported approach was the intramolecular Diels-Alder reaction of tetraene **2** that proceeded with only marginal stereoselection (55:45). Selective removal of the C(12)-C(13) double bond following cyclization was also problematic. Because Boeckman had reported that the Diels-Alder reaction of **3** proceeded with >100:1 stereoselection for a single trans-fused product,[2] we targeted the related TMS-substituted triene **4** as the key intermediate in an improved synthesis. *Much to our surprise, and in contrast to Boeckman's results, however, we found that the cyclization of 4 provided a 78:14:8 mixture of three cycloadducts.* This prompted us to broaden the scope of the present investigation and examine the effects of both the diene steric directing group X and the dienophile activating group[3] Y on the stereoselectivity of this key reaction (trienes **4-7**). In this way we hoped to define the optimal precursor to **1** and clearly evaluate the ability of substituents X and Y to influence intramolecular Diels-Alder stereoselectivity.[4]

Trienes **4-7** were synthesized as summarized in Scheme I.[5] Benzyl ether **8**, prepared as described previously from D-glyceraldehyde acetonide,[1] was smoothly elaborated to dibromo diene **9** ($[\alpha]^{23}_D$ -16.4° (*c* 1.0, $CHCl_3$)). After conversion[6] of **9** to the corresponding TMS alkyne, (iodovinyl)silane **10** ($[\alpha]^{23}_D$ -73.6° (*c* 1.1, $CHCl_3$)) was obtained via a hydroalumination-iodination sequence.[7] A very critical step followed, namely, the palladium-catalyzed cross-coupling reactions of **9** and **10** with vinylboronate **11**. Under the conditions described by Suzuki (aqueous 2 N NaOH, C_6H_6),[8] it was possible to prepare **12** ($[\alpha]^{23}_D$ -22.5° (*c* 1.0, $CHCl_3$)) and **13** ($[\alpha]^{23}_D$ -14.4° (*c* 1.2, $CHCl_3$)) in maximum yields of 55% and 36%, respectively. Considerable improvements, however, were realized by using the TlOH modification recently developed by Kishi.[9] Under optimal conditions, **12** (2 equiv each of **11** and TlOH, dioxane, 74%) and **13** (1.7 equiv each of **11** and TlOH, THF, 65%) were thus readily prepared. It is noteworthy that this synthesis of **13** represents the first successful example of a selective[10] mono-cross-coupling reaction of a 1,1-dibromo olefin[11] and may define a useful method for synthesis of 2-bromo 1,3-dienes for a range of synthetic objectives. Intermediates **12**/**13** were then elaborated to nitriles **14** ($[\alpha]^{23}_D$ -29.6° (*c* 0.9, $CHCl_3$)) and **15** ($[\alpha]^{23}_D$ -21.1° (*c* 1.2, $CHCl_3$)) by using Buchwald's zirconium-mediated hydrocyanation procedure[12] and finally to trienes **4** ($[\alpha]^{23}_D$ -21.2° (*c* 1.14, $CHCl_3$)), **5** [$(\alpha]^{23}_D$ -15.2° (*c* 2.67, $CHCl_3$)), **6**, and **7** via standard operations. It should be noted that alternative methods for synthesis of unsaturated aldehydes **6**/**7** involving Wittig or Petersen-type olefination procedures[12] gave considerably lower yields (43%) of less

(1) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327.
(2) Boeckman, R. K., Jr.; Barta, T. E. *J. Org. Chem.* **1985**, *50*, 3421.
(3) For previous studies of the effect of dienophile activating group on the stereoselectivity of intramolecular Diels-Alder reactions, see: Roush, W. R.; Essenfeld, A. P.; Warmus, J. *Tetrahedron Lett.* **1987**, *28*, 2447 and literature cited therein.
(4) For a related study, see: Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236.
(5) The spectroscopic properties (^{1}H NMR, IR, high-resolution mass spectrum) of all new compounds are in complete agreement with the assigned structures.
(6) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.
(7) (a) Hasan, I.; Kishi, Y. *Tetrahedron Lett.* **1980**, *21*, 4229. (b) On, H. P.; Lewis, W.; Zweifel, G. *Synthesis* **1981**, 999.
(8) Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972 and references therein.
(9) Uenishi, J.; Beau, J.-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.
(10) A single isomer was obtained. The stereochemistry was assigned by conversion of **13** to **12** (2 equiv of *t*-BuLi, THF, -78 °C, then TMSCl, 53%).
(11) (a) The high selectivity of this reaction was anticipated on the basis of the known rate difference for the palladium-catalyzed cross-couplings of (*E*)- vs (*Z*)-1-bromoalkenes: Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 2529. (b) While our work was in progress, the selective monosubstitution of 1,1-dichloroethylene was reported: Ratovelomanana, V.; Hammoud, A.; Linstrumelle, G. *Tetrahedron Lett.* **1987**, *28*, 1649. (c) See also: Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257. (d) For another recently reported example where a 1,1-dibromovinyl group undergoes a selective monosubstitution intramolecularly, see: Trost, B. M.; Chan, C.; Ruhter, S. *J. Am. Chem. Soc.* **1987**, *109*, 3486.
(12) Buchwald, S. L.; LaMaire, S. J. *Tetrahedron Lett.* **1987**, *28*, 295.

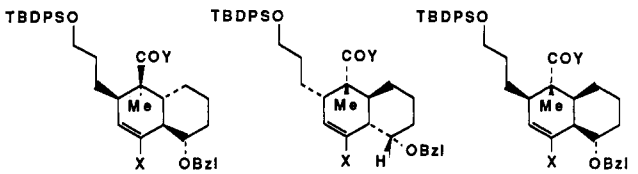
0022-3263/88/1953-0710$01.50/0

Scheme I



pure product than the lengthier sequence indicated in the scheme.

Mixtures of three cycloadducts were obtained in each of the Diels–Alder reactions summarized in Table I.[14,15] In this respect our data with TMS aldehyde 6 also differ from



16a, X = TMS, Y = OMe
16b, X = Br, Y = OMe
16c, X = TMS, Y = H
16d, X = Br, Y = H

17

18

results recently reported by Marshall for a related triene.[4,16] Nevertheless, our results clearly show that the TMS substituent induces better trans selectivity than Br under all conditions examined (compare entries 1 vs 2, 3 vs 6, and 5 vs 7). The same trend is readily apparent for CHO vs CO_2Me dienophile activation for bromo trienes **5** and **7** (entries 2, 6), but is surprisingly lacking for TMS trienes **4** and **6** (entries 1, 3). Significant improvement in trans stereoselectivity is realized in the Lewis acid catalyzed cyclizations of aldehydes **6** and **7**, but only the Et_2AlCl-catalyzed reaction of **6** is preparatively useful.

One area where the bromine substituent is superior to TMS is in the ability to induce equatorial configuration of the benzyloxy substituent. Thus, even though the trans selectivity of TMS trienes **4** and **6** is consistently superior to bromo trienes **5** and **7**, the *absolute selectivity* for the desired cycloadduct **16** is essentially the same in the thermal cyclizations of **4**, **6**, and **7**, a factor clearly reflected in the isolated yields of this diastereomer.

(13) (a) Schlessinger, R. H.; Poss, M. A.; Richardson, S.; Lin, P. *Tetrahedron Lett.* **1985**, *26*, 2391. (b) Corey, E. J.; Enders, P.; Block, M. G. *Tetrahedron Lett.* **1976**, 7.

(14) We cannot rule out the possibility that the fourth cycloadduct (epimer of **18**) was also produced but inadvertently escaped our notice.

(15) Stereostructural assignments for cycloadducts **16–18** rest on spectroscopic analyses and chemical conversions. Sequential treatment of **16b** ($[\alpha]^{23}_D$ −43.8° (*c* 1.1, $CHCl_3$)) with Na/Hg in MeOH and Bu_4NF in THF provided **1** ($[\alpha]^{23}_D$ −20.2° (*c* 0.92, $CHCl_3$)) in 76% yield (unoptimized), while treatment of **16a** ($[\alpha]^{23}_D$ −29.3° (*c* 2.39, $CHCl_3$), a 10:1 mixture with **17a**) with BF_3·Et_2O (20 equiv) and EtSH (55 equiv) in CH_2Cl_2 at 23 °C proceeded via **1** to the corresponding enantiomerically pure diol (82%), which was identical in all respects with the compound described in our previous publication (ref 1). Partial ^1H NMR data (obtained in C_6D_6 at 300 MHz) follows. **16a**: 6.39 (br d, J = 5.3 Hz, 1 H), 4.28 and 4.37 (benzylic AB, J =12.0 Hz, 2 H), 3.65 (m, 2 H), 3.42 (s, 3 H), 3.13 (dt, J = 3.6, 9.8 Hz, H_1), 1.27 (s, 3 H), 1.20 (s, 9 H), 0.94 (m, 1 H), 0.28 (s, 9 H). **17a** (not separable from **16a**; separation was achieved after BF_3·EtSH treatment): 6.15 (br dd, J = 5.3 Hz, H_7), 4.53 and 3.91 (benzylic AB, J = 14.3 Hz), 3.88 (br s, H_1), 2.88 (br t, J = 11.4 Hz, H_{4a}). **18a**: 6.40 (dd, J = 2.6, 3.9 Hz, 1 H), 4.57 and 4.51 (benzylic AB, J = 12.3 Hz, 2 H), 4.01 (m, including $J_{1,8a}$ = 2.6 Hz, H_1), 3.68 (m, 2 H), 3.39 (s, 3 H), 3.08 (m, H_6), 2.82 (m, H_{8a}), 2.72 (m, including $J_{4a,8a}$ = 3.8 Hz, H_{4a}), 1.27 (s, 3 H), 1.21 (s, 9 H), 0.14 (s, 9 H). **16b**: 6.22 (dd, J = 4.1, 3.0 Hz, H_7), 4.25 and 4.78 (benzylic AB, J = 11.7 Hz), 3.58 (m, 2 H), 3.34 (s, 3 H), 3.31 (m, including $J_{1,8a}$ = 10.6 Hz, H_1), 2.26 (br t, J = 10.6 Hz, H_{8a}), 2.06 (br t, J = 10.6 Hz, H_{4a}), 1.19 (s, 9 H), 1.14 (s, 3 H). **17b** (not separable from **18b**): 6.05 (br s, H_7), 4.05 (br dd, J = 3.6 Hz, H_1), 2.11 (br t, J = 8 Hz, H_{4a}). **18b**: 6.35 (br t, H_7), 4.32 and 4.42 (benzylic AB, J = 12.7 Hz, 2 H), 4.32 (br s, H_1), 3.59 (m, 2 H), 3.31 (s, CH_3), 3.07 (m, H_6), 2.97 (br s, H_{8a}), 2.73 (br dt, $J_{4a,4ax}$ = 11.2 Hz, H_{4a}), 1.20 (s, 9 H), 1.11 (s, 3 H). **16c**: 9.49 (s, 1 H), 6.29 (dd, J = 2.2, 4.4 Hz, H_7), 4.25 and 4.41 (benzylic AB, J = 12.7 Hz, 2 H), 3.59 (m, 2 H), 3.08 (dt, J = 3.9, 9.2 Hz, H_1), 2.04 (br t, $J_{4a,8a}$ = 9.3 Hz, H_{8a}), 1.88 (m, H_6), 1.76 (dt, H_{4a}), 1.21 (s, 9 H), 0.99 (s, 3 H), 0.82 (br dq, H_{4ax}), 0.26 (s, 9 H). **17c** (not separable from **16c**): 9.56 (s, 1 H), 6.13 (dd, J = 2.4 Hz, H_7), 4.42 and 4.24 (benzylic AB, J = 12 Hz, 2 H), 3.93 (br s, H_1), 2.78 (dt, J = 2, 11 Hz, H_{4a}), 0.13 (s, 9 H). **18c**: 9.22 (s, 1 H), 6.32 (dd, $J_{6,7}$ = 3.0 Hz, H_7), 4.42 and 4.52 (benzylic AB, J = 14.7 Hz, 2 H), 3.98 (br s, $J_{1,8a}$ = 2.1 Hz, H_1), 3.67 (m, 2 H), 2.67 (m, H_6), 2.63 (m, H_{8a}), 2.27 (dt, $J_{4a,8a}$ = 2.9 Hz, $J_{4a,4ax}$ = 12 Hz, H_{4a}), 1.20 (s, 9 H), 0.77 (s, 3 H), 0.08 (s, 9 H). **16d**: 9.25 (s, 1 H), 6.12 (dd, J = 5.3, 1.8 Hz, H_7), 4.27 and 4.78 (benzylic AB, J = 11.9 Hz, 2 H), 3.52 (br t, 2 H), 3.25 (br dt, including $J_{1,8a}$ = 9 Hz, H_1), 2.18 (br t, J = 10 Hz, H_{8a}), 1.88 (m, H_2), 1.78 (dt, J = 2.8, 10.5 Hz, H_{4a}), 1.65 (m, H_6), 1.20 (s, 9 H), 1.06 (m, H_{3ax}), 0.85 (s, 3 H), 0.72 (dq, H_{4ax}). **17d** (structural assignment is tentative; this material detected in crude mixtures only): 9.06 (s, 1 H), 6.05 (dd, H_7). **18d**: 9.00 (s, 1 H), 6.25 (br t, J = 4 Hz, H_7), 4.20 and 4.31 (benzylic AB, J = 11.7 Hz, 2 H), 4.24 (m, H_1), 3.57 (m, 2 H), 2.73 (br s, including $J_{4a,8a}$ = 3.9 Hz), 2.57 (m, H_6), 2.23 (br dt, J = 8.2, 3.9 Hz, H_{4a}), 1.20 (s, 9 H), 0.59 (s, 3 H).

Table I. Intramolecular Diels–Alder Reactions of 4–7

entry	triene	conditions[a]	16:17:18[b]	trans:cis[c]	eq:ax[d]	combined yield,[e] %	yield of 16,[e] %
1	**4**	160 °C	78:8:14	86:14	10:1	85	66[f]
2	**5**	160 °C	62:4:34	66:34	15:1	80	50
3	**6**	160 °C	79:9:12	88:12	9:1	82	65[f]
4	**6**	Et_2AlCl, −15 °C	89:5:6	94:6	18:1	77	68[f]
5	**6**	$EtAlCl_2$, −40 °C	90:5:5	95:5	18:1	32	28[f]
6	**7**	160 °C	75:3:22	78:22	25:1	86	64
7	**7**	$EtAlCl_2$, −15 °C	90:1:9	91:9	90:1	24	22
8	**7**	Et_2AlCl, 23 °C			no reaction		

[a] Thermal reactions were performed in toluene (0.01 M) under N_2 with BHT added. Lewis acid catalyzed reactions were performed in CH_2Cl_2 with 0.95 equiv of reagent. [b] Product ratios were determined by ^1H NMR analysis (C_6D_6) of crude product mixtures or of partially purified samples (care being taken not to fractionate the diastereomers). [c] Ratio of **16** + **17** versus **18**. [d] Ratio of **16** to **17**. [e] Yields of products purified by chromatography. [f] Yield corrected for the presence of **17** which is not separable from **16** under the chromatography conditions employed.

From the standpoint of defining the optimal precursor to **1**, issues other than the stereoselectivity of this key cyclization must be considered. With dibromovinyl compound **9** as the point of reference, the syntheses of trienes **4**–**7** proceed as follows: **4**, 6 steps (23% yield overall); **5**, 4 steps (42%); **6**, 8 steps (21%); and **7**, 6 steps (38%). Thus, in terms of ease of triene preparation (length and yield of synthesis), yield of cycloadduct **16**, and ease of functional group manipulation following cyclization,[1,2] and given the method of synthesis reported here, bromo triene **5** is, in fact, the optimal precursor to **1**. That is, the brevity and and efficiency of the synthesis of **5** compensates for the fact that it is the least selective Diels–Alder substrate. Efforts to complete a chlorothricolide synthesis along these lines will be reported in due course.

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(16) In the cyclizations of **4** and **6**, the two trans-fused epimers (**16a**–**17a** and **16c**–**17c**) moved considerably more rapidly on TLC (R_f 0.45, 9:1 hexane–Et_2O; these epimers did not resolve in this system) than the cis-fused isomers (**18a,c**; R_f 0.3). Such a large difference in TLC mobility was not observed with the cyclization products of **5** and **7**. It is conceivable that the product corresponding to **18c** was inadvertently separated during Marshall's chromatographic cleanup prior to diastereomer analysis (ref 4).