A Stereospecific Synthesis of (Z)-δ-Halo-γ,δ-unsaturated Ketones via Haloboration Reaction of Terminal Alkynes[1]

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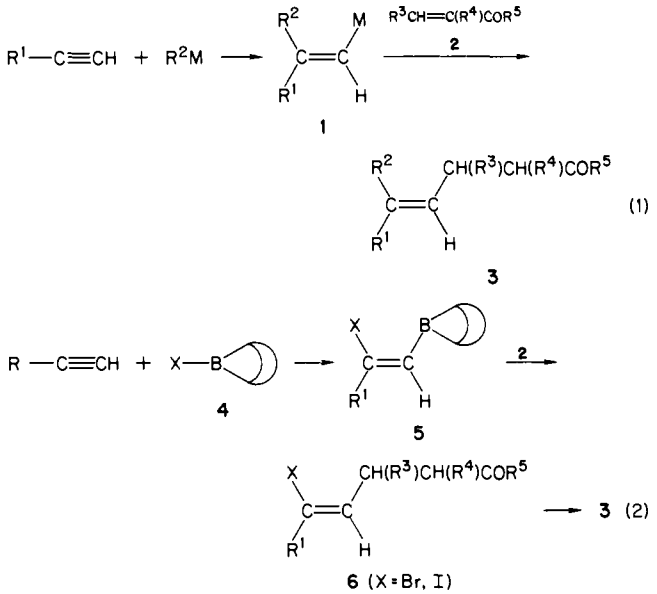
Abstract: Michael-type reactions of (*Z*)-β-bromo- and iodoalkenyl-9-borabicyclo[3.3.1]nonanes (**5**), readily available by haloboration of 1-alkynes, with acyclic α,β-unsaturated ketones (**2**) in a nonpolar solvent under Lewis acidic conditions are presented. The products, (*Z*)-δ-halo-γ,δ-unsaturated ketones (**6**), are obtained in stereochemically pure form (>98%). Since the haloalkenylboranes (**5**) are prepared in situ from haloboranes (**4**) and 1-alkynes, the present reaction provides a stereospecific, one-pot, and general synthesis of the title compounds (**6**). When methyl vinyl ketone (MVK) is used as the Michael acceptor, aldol condensation of the intermediate boron enolate with an excess of MVK occurs. However, the aldol (**7**) is transformed into the parent haloenone (**6′**) without difficulty upon subsequent, in situ treatment with a base. The same product (**6′**) is prepared directly by the reaction with 3-(trimethylsilyl)-3-buten-2-one. Synthetic utility of the present method is demonstrated by selective syntheses of several natural products. Sulcatol (**11**) is obtained in an overall yield of 63% starting from propyne. In a similar manner, *trans*-geranyl acetone (**14**) and *trans*-nerolidol (**15**) are prepared stereospecifically (>98%) in 62 and 72% yields, respectively, from 6-methyl-5-hepten-1-yne (**12**).

δ,δ-Disubstituted-γ,δ-unsaturated ketones (**3**) have been reported to be important intermediates in the synthesis of natural products such as terpenoids.[2] One of the methodologies for the straightforward synthesis of such compounds (**3**) is carbometalation of 1-alkynes[3] followed by conjugate addition of the resultant alkenylmetallics (**1**) to α,β-unsaturated ketones (**2**) (eq 1). However, such Michael-type additions have serious defects because of the inapplicability to readily polymerizable acyclic α,β-unsaturated ketones (**2**).[4] Fortunately, organoborane derivatives are well-known to give good results even for acyclic enones (**2**),[5] although there is no direct and general method to synthesize the intermediate β,β-disubstituted alkenylboranes (**1**, M = B).[6]



(1) Organic Synthesis Using Haloboration Reaction. Part 7.

(2) Heathcock, C. H.; Graham, S.; Pirrung, M. C.; Plavac, F.; White, C. T. "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1983; Vol. 5, Chapter 2.

(3) For review, see: Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–870.

(4) (a) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888–3901. (b) Hooz, J.; Layton, R. B. *Can. J. Chem.* **1973**, *51*, 2098–2102. See also ref 3.

(5) Alkyl-, alkenyl-, and alkynylboranes are all known to react readily with acyclic α,β-unsaturated ketones in the 1,4-addition manner. (a) Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H. C.; Rogic, M. M.; Rathke, M. W. *J. Am. Chem. Soc.* **1967**, *89*, 5708–5709. (b) Kabalka, G. W.; Brown, H. C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* **1970**, *92*, 710–712. (c) Alkenylboranes; Jacob, P.; Brown, H. C. *J. Am. Chem. Soc.* **1976**, *98*, 7832–7833. (d) Alkynylboranes: Sinclair, J. A.; Molander, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1977**, *99*, 954–956.

Herein, we wish to report a conjugate addition reaction of B-(*Z*)-β-haloalkenyl-9-borabicyclo[3.3.1]nonanes (B-haloalkenyl-9-BBN's, **5**) with acyclic α,β-enones (**2**) to give (*Z*)-δ-halo-γ,δ-unsaturated ketones (**6**) (eq 2). Due to the recent development of transition-metal-promoted cross-coupling reactions between alkenyl halides and various organometallics,[7] the haloenones (**6**) will serve as useful and versatile intermediates for the synthesis of **3**.

Recently, we have found that the haloboration of terminal alkynes with B-bromo- or B-iodo-9-BBN (**4**)[8] proceeds highly regio- and stereoselectively (>98%) to afford the syn adducts, B-(*Z*)-β-haloalkenyl-9-BBN's (**5**), in essentially quantitative yields.[9] The haloalkenylboranes (**5**) thus formed are, however, far less reactive than the simple alkenylboranes obtained by hydroboration of 1-alkynes, presumably owing to the electronegative halogen substituent. Thus, the reaction of B-(*Z*)-2-bromo-1-heptenyl-9-BBN (**5**, R = C_5H_{11}, X = Br) with methyl vinyl ketone (MVK) gives the desired haloenone (**6′**) in a poor yield (≃10%) under the conditions employed for B-alkenyl-9-BBN's (reflux in THF).[5c]

In sharp contrast, we found that the reaction takes place smoothly under Lewis acidic conditions (in pentane, 100% excess of B-X-9-BBN). Quite unexpectedly, the major product isolated after the reaction with MVK under the aforementioned conditions was not the enone (**6′**) but the aldol (**7**). No aldol adducts were formed in the case of enones other than MVK. Although attempts to circumvent the unexpected aldol condensation were unsuccessful, the adduct (**7**) was found to undergo selective retro-aldol condensation when heated with a base (NaOH) (eq 3).[10] As

(6) An indirect method which involves a transmetalation reaction of alkenyl groups from Al to B has been reported: Negishi, E.-i.; Boardman, L. D. *Tetrahedron Lett.* **1982**, *23*, 3327–3330.

(7) (a) Collman, J. P.; Hegedus, L. S. "Principles and Applications of Organotransition Metal Chemistry"; University Science Books: Mill Valley, 1980. (b) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340–348. (c) Davies, S. G. "Organotransition Metal Chemistry: Applications to Organic Synthesis"; Pergamon Press: Oxford, 1982. (d) Hegedus, L. S. "Group VIII Transition Metals in Organic Synthesis" In "Modern Synthetic Methods"; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt am Main, 1983; Vol. 3, pp 61–138. (e) Posner, G. H. "An Introduction to Synthesis Using Organocopper Reagents"; Wiley: New York, 1980; pp 72–74. (f) Tsuji, J. "Organic Synthesis with Palladium Compounds"; Springer Verlag: Berlin, 1980. (g) Jolly, P. W. "Nickel Catalyzed Coupling of Organic Halides and Related Reactions" In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 8, pp 713–798. (h) Trost, B. M. "Organopalladium Compounds in Organic Synthesis and in Catalysis" In "Comprehensive Organometallic Chemistry"; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 8, pp 799–938.

(8) Brown, H. C.; Kulkarni, S. U. *J. Organomet. Chem.* **1979**, *168*, 281–293.

(9) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731–734.

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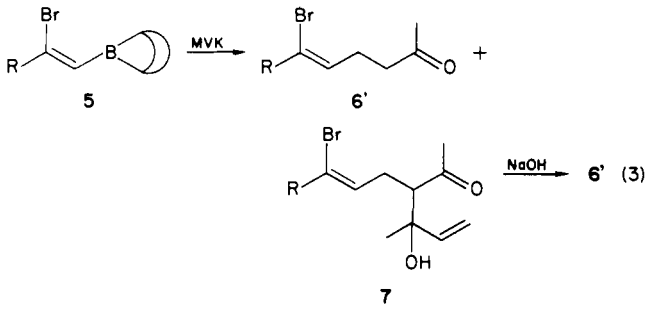
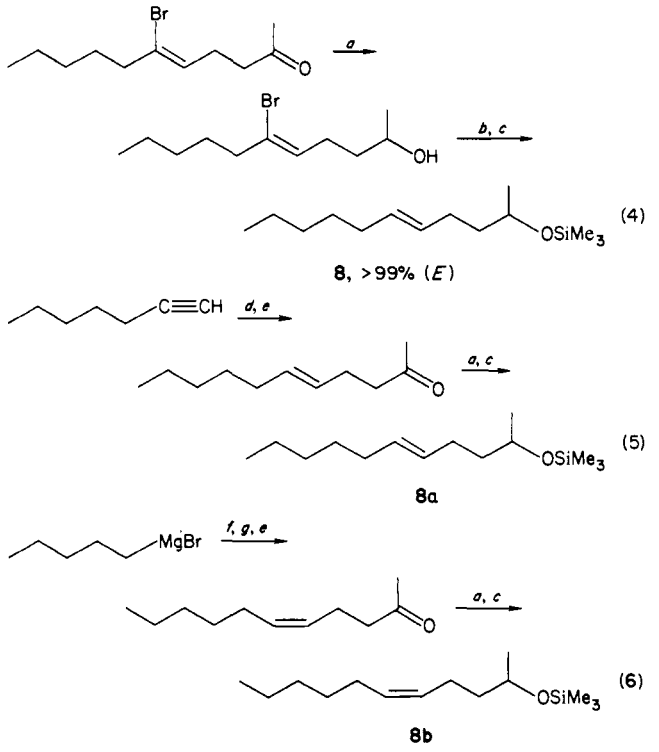
shown in Table I, the present method provides a general route to the haloenones (**6**) inaccessible by conventional procedures,[11]



Since the ^1H NMR spectra of all the haloenones (**6**) showed only a single kind of vinylic signal, high stereoselectivity of the present process is readily verified. Furthermore, the stereochemical consequence was unambiguously determined by transforming a bromoenone (**6'**, R = C_5H_{11}, X = Br) into the corresponding debrominated silyl ether (**8**) (eq 4). Two authentic olefinic isomers (**8a** and **8b**) were prepared via the known (*E*)-[5c] and (*Z*)-enones[4a] (eq 5 and 6). Direct comparison of these three samples on a capillary GLPC (Apiezon L, 45 m) revealed that the silyl ether (**8**) obtained from our bromoenone contained the (*E*) isomer more than 99%, indicating the stereospecific nature of this Michael reaction.[5c]



[a] $NaBH_4$. [b] *sec*-BuLi (3.0 eq), −78 °C, 1 h, then MeOH. [c] Me_3SiCl, $(Me_3Si)_2NH$, pyridine. [d] 9-BBN. [e] MVK, reflux for 14 h. [f] $CuBr \cdot Me_2S$. [g] $HC{\equiv}CH$.

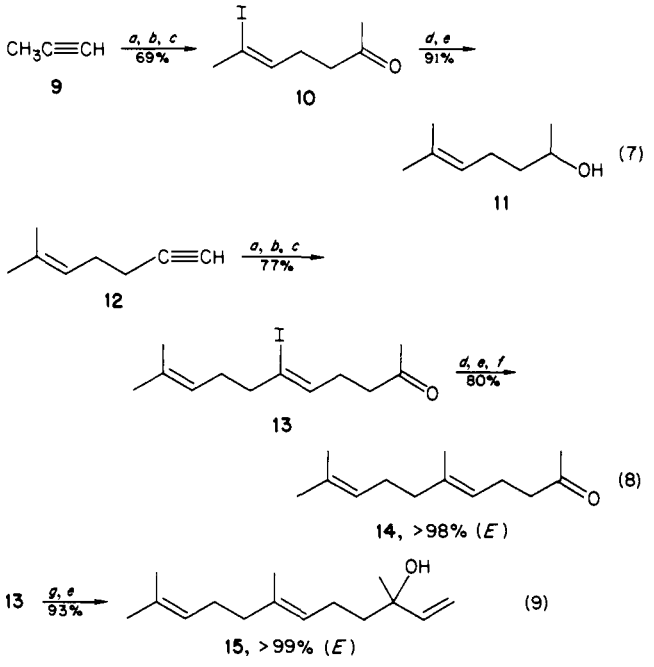
The reaction with α-(trimethylsilyl)butenone[12] deserves a comment since it gives the 1,4-adduct (**6'**) directly without retro-aldol treatment. This enone is quite useful for the substrates bearing heat- and/or base-sensitive groups (see entry 9 in Table I).

(10) Care should be taken that the aldol (**7**) decomposes to **6'** and MVK quantitatively upon GLPC analysis. However, the progress of the retro-aldol condensation can be pursued by TLC analysis, on which the aldol (**7**) appears as a spot of a lower R_f value than **6'**.

(11) Salino, R. F.; Berson, J. A. *J. Am. Chem. Soc.* **1982**, *104*, 2228–2232.

(12) Boeckman, R. K.; Blum, D. M.; Ganem, M.; Harvey, N. *Org. Synth.* **1977**, *58*, 152–157.

The present haloboration–conjugate addition sequence was applied to the synthesis of several natural products. For instance, propyne (**9**) was converted to the iodoenone (**10**) by a modified procedure (see Experimental Section) in 69% yield. Reduction of **10** with $NaBH_4$ and subsequent methylation (6 equiv of $LiCuMe_2$, 2,5 days) afforded sulcatol (**11**), an aggregation pheromone of an ambrosia beetle, in 91% yield from **10** (eq 7). The carbocupration approach to **11** proceeds in less than 25% from **9**.[4a] High chemoselectivity of the haloboration reaction allows us to synthesize the olefinic iodoketone (**13**), from which *trans*-geranylacetone (**14**) and *trans*-nerolidol (**15**) were synthesized in excellent yields and stereoselectivities[13] as illustrated in eq 8 and 9. Further investigations of haloboration reaction and their applications are under way.



[a] B-I-9-BBN. [b] MVK. [c] aqueous NaOH, heat. [d] $NaBH_4$. [e] $LiCuMe_2$. [f] PCC. [g] $CH_2{=}CHMgBr$.

Experimental Section

Materials. B-Halo-9-borabicyclo[3.3.1]nonanes,[8] 1-hexyne,[14] 1-heptyne,[14] 1-octyne,[14] 1-decyne,[14] 3-(trimethylsilyl)-3-buten-2-one,[12] and 6-methyl-5-hepten-1-yne[15] were prepared according to the literature procedures. Propyne (Tokyo Kasei), phenylethyne (Tokyo Kasei), benzalacetone (Wako Pure Chemicals), and chalcone (Wako Pure Chemicals) were used without further purification. Pentane was distilled from sodium metal prior to use. Methyl vinyl ketone (Tokyo Kasei) and propargyl bromide (Tokyo Kasei) were distilled before use.

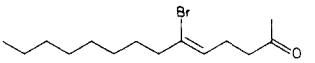
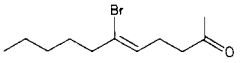
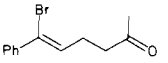
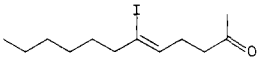
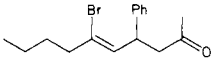
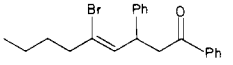
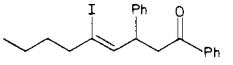
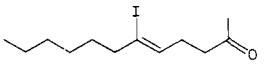
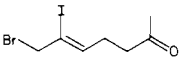
(*Z*)-6-Bromo-5-tetradecen-2-one: Typical Procedure for Michael Addition–Retro-Aldol. To a dry 50-mL round-bottomed vessel equipped with a septum inlet, a magnetic stirring bar, a Dimroth-type condenser, a three-way cock, and a nitrogen inlet were added 0.37 g of B-bromo-9-BBN (1.84 mmol) and 5 mL of pentane under an atmosphere of nitrogen. 1-Decyne (0.127 g, 0.92 mmol) was added to the stirred mixture

(13) Determined by the comparison with authentic samples, which consists of (*E*) and (*Z*) isomers (ca. 9:1).

(14) Brandsma, L.; Verkruijsse, H. D. "Synthesis of Acetylenes, Allenes and Cumulenes"; Elsevier Scientific: Amsterdam, 1981.

(15) (a) Sondheimer, F.; Wolovski, R.; Ben-Efraim, D. A. *J. Am. Chem. Soc.* **1961**, *83*, 1686–1691. (b) Sato, K.; Inoue, S.; Ota, S. *J. Org. Chem.* **1970**, *35*, 565–566. (c) Whitesell, J. K.; Fisher, M.; Jardine, P. D. S. *J. Org. Chem.* **1983**, *48*, 1556–1557. None of these reported methods were satisfactory in view of convenience[15b,c] or product purity[15a] for the preparation of this alkyne. We have found that the allenyl Gringnard route[15a] can be utilized if the workup procedure is modified. Crude 6-methyl-5-hepten-1-yne,[15a] contaminated by an appreciable amount of allenic isomer, was treated with an excess of ethylmagnesium bromide in ether (reflux, 3 h) and then thoroughly evacuated (oil-pump vacuum, 50 °C, 1 h) to ensure complete removal of non-acetylenic components. Careful decomposition of the remaining solid with a saturated solution of aqueous ammonium chloride followed by distillation through a 40-cm Vigreux column affords the enyne of high purity (>97% by GLPC).

Table I. Synthesis of (*Z*)-δ-Halo-γ,δ-unsaturated Ketones (6)

entry	X	alkyne	enone	product[a]	yield,[b] %	isomeric purity,[c] %
1	Br	1-decyne	MVK[e]		83	99
2	Br	1-heptyne	MVK[e]		83	99
3	Br	phenylethyne	MVK[e]		83	99
4	I	1-octyne	MVK[e]		92	99
5	Br	1-hexyne	$PhCH{=}CHCOCH_3$		64	98[d]
6	Br	1-hexyne	PhCH=CHCOPh		72	98[d]
7	I	1-hexyne	PhCH=CHCOPh		79	99[d]
8	I	1-octyne	$CH_2{=}C(SiMe_3)COCH_3$		52[f]	99
9	I	$BrCH_2C{\equiv}CH$	$CH_2{=}C(SiMe_3)COCH_3$		80[f]	99

[a] All the products were adequately characterized by spectroscopic and analytical means. [b] Isolated yields based on the starting 1-alkynes. [c] Determined by GLPC. [d] Determined by ^1H NMR. [e] After the reaction with MVK, the mixture was treated with a base to effect retro-Aldol condensation. See text. [f] The Me_3Si group was cleaved during workup.

dropwise at room temperature, and stirring was continued for 1 h. Then MVK (0.19 g, 2.76 mmol) was introduced (slightly exothermic) and the resultant yellow solution was stirred further for 2 h. The volatile materials were removed under vacuum, and the remaining oil was dissolved in 5 mL of toluene. After addition of 2 mL of aqueous 3 M NaOH, the mixture was heated at ca. 100 °C for 14 h and then extracted with ether. The extracts were washed with water and brine, dried over $MgSO_4$, and evaporated. Purification of the residual oil by preparative TLC (silica gel, hexane/methylene chloride) gave 0.221 g of the title bromoenone (83% yield based on 1-decyne): n^{20}_D 1.4802; IR (film) 2960, 1720, 1360, 1155 cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (t, 3 H, *J* = 6 Hz), 1.1–1.7 (m, 12 H), 2.07 (s, 3 H), 2.2–2.6 (m, 6 H), 5.70 (t, 1 H, *J* = 6 Hz); MS, *m/e* (M^+ - Br) 209. Anal. Calcd for $C_{14}H_{25}OBr$: C, 58.13; H, 8.71. Found: C, 58.32; H, 8.82

(*Z*)-6-Bromo-5-undecen-2-one: n^{20}_D 1.4821; IR (film) 2940, 2850, 1715, 1655, 1358, 1160, 1115 cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (t, 3 H, *J* = 7 Hz), 1.1–1.8 (m, 6 H), 2.02 (s, 3 H), 2.2–2.6 (m, 6 H), 5.58 (t, 1 H, *J* = 7 Hz); MS, *m/e* (M^+ - Br) 151. Anal. Calcd for $C_{11}H_{19}OBr$: C, 53.45; H, 7.75; Br, 32.33. Found: C, 53.63; H, 7.83; Br, 32.21.

(*Z*)-1-Bromo-1-phenyl-1-hexen-5-one: n^{20}_D 1.5641; IR (film) 2840, 1715, 1485, 1355, 1155, 860, 770, 685 cm^{-1}; ^1H NMR (CCl_4) δ 2.08 (s, 3 H), 2.5–2.6 (m, 4 H), 6.19 (t, 1 H, *J* = 7 Hz), 7.1–7.5 (m, 5 H); MS, *m/e* (M^+ - Br) 174. Anal. Calcd for $C_{12}H_{13}OBr$: C, 56.94; H, 5.18. Found: C, 57.05; H, 5.28.

(*Z*)-6-Iodo-5-dodecen-2-one: n^{20}_D 1.5060; IR (film) 2970, 2680, 1715, 1375, 1155, 1110 cm^{-1}; ^1H NMR (CCl_4) δ 0.85 (t, 3 H, *J* = 6 Hz), 1.1–1.7 (m, 8 H), 2.00 (s, 3 H), 2.1–2.6 (m, 6 H), 5.45 (t, 1 H, *J* = 7 Hz); MS, *m/e* (M^+ - I) 181. Anal. Calcd for $C_{12}H_{21}OI$: C, 46.92; H, 6.89; I, 41.32. Found: C, 46.80; H, 6.97; I, 41.47.

(*Z*)-6-Iodo-10-methyl-5,9-undecadien-2-one (13): n^{20}_D 1.5199; IR (film) 2960, 2920, 2840, 2715, 1640, 1355, 1155 cm^{-1}; ^1H NMR (CCl_4) δ 1.62 (s, 3 H), 1.65 (s, 3 H), 2.06 (s, 3 H), 2.1–2.6 (m, 8 H), 5.01 (t, 1 H, *J* = 7 Hz), 5.50 (t, 1 H, *J* = 7 Hz); MS, *m/e* (M^+ - I) 179. Anal. Calcd for $C_{12}H_{19}OI$: C, 47.07; H, 6.25; I, 41.44. Found: 47.06; H, 6.31; I, 41.37.

(*Z*)-2-Iodo-2-hepten-6-one (10). A round-bottomed flask equipped with a magnetic stirring bar, a septum cap, a cold-finger trap (directly connected to the top of the flask), and a nitrogen inlet was charged with 0.71 g of B-iodo-9-BBN (3.0 mmol) and 10 mL of pentane under nitrogen. In a separate graduated tube, 6.0 mmol of propyne was collected from a cylinder at −78 °C. Propyne was transferred to the reaction flask, whose cold-finger trap was kept at −78 °C by means of a double-tipped needle. The reaction mixture was stirred during the addition of propyne and then further for 1 h. MVK (9.0 mmol) was introduced via a syringe and a whole mixture was agitated magnetically for 2 h. Retro-aldol operations were performed as mentioned in the Typical Procedure. Purification of the remained oil by column chromatography (silica gel, hexane/methylene chloride) afforded 0.492 g of the iodoenone (69% from B-iodo-9-BBN): n^{20}_D 1.5269; IR (film) 2940, 1715, 1650, 1440, 1360, 1155, 1100, 1030 cm^{-1}; ^1H NMR (CCl_4) δ 2.05 (s, 3 H), 2.2–2.6 (m, 4 H), 2.46 (s, 3 H), 5.45 (t, 1 H, *J* = 7 Hz); MS, *m/e* (M^+ - I) 111. Anal. Calcd for $C_7H_{11}OI$: C, 35.32; H, 4.66; I, 53.31. Found: C, 35.48; H, 4.66; I, 53.58.

(*Z*)-6-Bromo-4-phenyl-5-decen-2-one. This compound was obtained by the reaction with benzalacetone according to the Typical Procedure without the retro-aldol operations: n^{20}_D 1.5995; IR (film) 2950, 2930, 2850, 1685, 1590, 1490, 1440, 750, 690 cm^{-1}; ^1H NMR (CCl_4) δ 0.88 (t, 3 H, *J* = 6 Hz), 1.0–1.8 (m, 4 H), 1.98 (s, 3 H), 2.38 (t, 2 H, *J* = 7 Hz), 2.66 (d, 1 H, *J* = 7 Hz), 2.70 (d, 1 H, *J* = 7 Hz), 4.0–4.5 (m, 1 H), 5.71 (d, 1 H, *J* = 9 Hz), 6.7–7.8 (m, 5 H); MS, *m/e* (M^+ - Br) calcd for $C_{16}H_{21}O$ 229.1592, obsd 229.1596.

(*Z*)-5-Bromo-1,3-diphenyl-4-nonen-1-one. The reaction with chalcone gave the bromoenone without retro-aldol treatment: n^{20}_D 1.5761; IR (film) 2950, 2925, 1685, 1590, 1575, 1490, 1440, 740, 690 cm^{-1}; ^1H NMR (CCl_4) δ 0.86 (t, 3 H, *J* = 6 Hz), 1.0–1.7 (m, 4 H), 2.37 (t, 2 H, *J* = 8 Hz), 3.22 (d, 1 H, *J* = 7 Hz), 3.28 (d, 1 H, *J* = 7 Hz), 4.2–4.6 (m, 1 H), 5.80 (d, 1 H, *J* = 9 Hz), 6.7–7.9 (m, 10 H); MS, *m/e* (M^+ - Br) calcd for $C_{21}H_{23}O$ 291.1748, obsd 291.1745.

(*Z*)-5-Iodo-1,3-diphenyl-4-nonen-1-one: n^{20}_D 1.5940; IR (film) 2970, 2940, 2860, 1690, 1600, 1580, 1495, 1450, 750, 695 cm^{-1}; ^1H NMR (CCl^4) δ 0.89 (t, 3 H, *J* = 6 Hz), 1.0–1.6 (m, 4 H), 2.44 (t, 2 H, *J* = 7 Hz), 3.27 (d, 1 H, *J* = 7 Hz), 3.32 (d, 1 H, *J* = 7 Hz), 4.0–4.4 (m, 1 H), 5.70 (d, 1 H, *J* = 9 Hz), 6.7–8.0 (m, 10 H); MS, *m/e* (M^+ - I) 291. Anal. Calcd for $C_{21}H_{23}OI$: C, 60.30; H, 5.54; I, 30.34. Found: C, 60.33; H, 5.55; I, 30.12.

(*Z*)-1-Bromo-2-iodo-2-hepten-6-one. Iodoboration of propargyl bromide with B-iodo-9-BBN followed by the reaction with the silylbutenone[12] afforded this dihalide in 80% yield: n^{20}_D 1.5612; IR (film) 2940, 1725, 1635, 1425, 1370, 1215, 1170 cm^{-1}; ^1H NMR (CCl_4) δ 2.04 (s, 3 H), 2.2–2.6 (m, 4 H), 4.17 (s, 2 H), 5.89 (t, 1 H, *J* = 7 Hz); MS, *m/e* (M^+ - Br) calcd for $C_7H_{10}OI$ 236.9779, obsd 236.9791.

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Registry No. 9, 74-99-7; **10**, 97071-82-4; (±)-**11**, 4630-06-2; **12**, 22842-10-0; **13**, 97071-77-7; **14**, 3796-70-1; (±)-**15**, 2211-29-2; MVK, 78-94-4; $PhCH{=}CHCOCH_3$, 122-57-6; PhCH=CHCOPh, 94-41-7;

CH_2=C($SiMe_3$)$COCH_3$, 43209-86-5; (Z)-n-C_8H_{17}C(Br)=CH-$(CH_2)_2COCH_3$, 97071-73-3; (Z)-n-C_5H_{11}C(Br)=CH$(CH_2)_2COCH_3$, 97071-74-4; (Z)-PhC(Br)=CH$(CH_2)_2COCH_3$, 97071-75-5; (Z)-n-C_6H_{13}C(I)=CH$(CH_2)_2COCH_3$, 97071-76-6; (Z)-n-C_4H_9C(Br)=CHCHPhCH_2COCH_3, 97071-78-8; (Z)-n-C_4H_9C(Br)=CHCHPhCH_2COPh, 97071-79-9; (Z)-n-C_4H_9C(I)=CHCHPhCH_2COPh, 97071-80-2; (Z)-BrCH_2C(I)=CH$(CH_2)_2COCH_3$, 97071-81-3; CH_2=CHBr, 593-60-2; 1-decyne, 764-93-2; 1-heptyne, 628-71-7; phenylethyne, 536-74-3; 1-octyne, 629-05-0; 1-hexyne, 693-02-7; propargyl bromide, 106-96-7.

Supplementary Material Available: Syntheses and spectral data of compounds **7** (R = C_8H_{17}), **11**, **14**, and **15** (3 pages). Ordering information is given on any current masthead page.

A Logic-Based Program for Synthesis Design

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Abstract: A minicomputer program (SYNGEN) is described which generates all variable syntheses for any target structure within defined constraints and without user interaction. SYNGEN first dissects the skeleton to find all fully convergent bondsets which utilize available starting material skeletons found in (usually) only two successive levels of cuts. Then for each such bondset the necessary functionality is generated to initiate successive constructions of each designated bond, from real starting materials to the target functionality. The construction reactions are generated from mechanistic principles formulated in a generalized digital description and requiring no database library. The output is displayed by a second program (SYNOUT) which allows examination and selection of the resulting routes. Several examples are discussed showing actual syntheses reproduced as well as new routes equally short.

I. Introduction and Overview

We have discussed previously some new logical tenets for approaching a viable system for synthesis design.[1] This paper describes a working minicomputer program embodying those tenets. The program has two parts: first, a skeletal dissection of the target, second, a generation of functionality necessary to assemble the synthons so defined. In this paper we present an overview of goals, methods, and results as well as a discussion of skeletal dissection. The characteristics of the approach are summarized here and amplified below: (1) an executive program not interactive with the chemist; (2) assessment of all possible routes within clearly defined constraints; (3) digital expression of molecules and reactions; (4) initial skeletal dissection for efficient assembly; (5) orientation on available starting materials; (6) orientation on economy of steps; (7) limitation primarily to construction reactions; (8) generation of reactions from mechanistic logic; (9) no prediction of yields.

An executive program assures that the given set of rules and heuristics are consistently applied in all cases without operator bias so that all possible routes will be generated and assessed by the same criteria. The operator, of course, selects from the final output of a few optimal routes, but only after execution of the program is complete. The molecules and reactions are all expressed and manipulated as simple lists of digits expressing functionality. This serves to increase computer speed and lessen storage considerably, but more importantly it assures that all possible results are simply mathematical combinations and hence readily ascertained. Furthermore, the digital expression serves to abstract the essentials and coalesce trivial distinctions of functionality, making it possible to span the enormous potential search space of the problem.

The first operation of the program is to examine ways to break up the skeleton into the fewest pieces, or synthon skeletons, which actually exist as starting materials, thus defining optimal bondsets.[1,2] In the dichotomy of skeleton vs. functionality, we focus on the skeleton as first consideration, rather than an examination of target functionality to ascertain all possible last reactions to form it. We suspect this prior skeletal examination to be a very common mode of perception among synthetic chemists. It also has the advantage of formulating rational routes to saturated hydrocarbons and, even in functionalized targets, of discerning where to use dummy functional groups that are eliminated en route and leave no trace in the target functionality.

An ordered bondset[2] dictates the starting skeletons and is indeed the simplest overall description of any synthesis conceptually. Thus the search is focused to strike through the massive center of the synthesis tree, rooting the search on available starting material skeletons and so allowing it to converge rapidly. An ordered catalog of available starting materials is an important ensemble of data for the process of synthesis design and it can be used actively in this way to focus the selection of pathways. Our program interacts at present with a catalog of about 5000 basic starting materials, which represent 344 skeletons of connected C and N atoms.[3]

The central criterion of the program is economy, expressed as the fewest steps or operations in the most convergent order.[4] An ordered bondset shows both the number of constructions needed and the extent of convergency involved in assembling the skeleton. This is the key to assembling the target molecule in the most efficient way. Construction reactions are obligatory to the assembly but other reactions are not, and the intent of the program is to seek routes which are primarily composed of construction reactions. Other reactions are, however, included or implicit, especially when they are attendant on the constructions, as described in section IIIB below.

The number of synthetic reactions available is probably in the tens of thousands, depending on the detail of definition, and is constantly growing. Incorporation of a library of reactions in the

(1) Hendrickson, J. B.; Braun-Keller, E.; Toczko, A. G. *Tetrahedron, Suppl.* **1981**, *37*, 359.

(2) A *bondset* is the set of skeletal bonds actually constructed in any given synthesis.[1] An *ordered bondset* defines the order in which they are constructed as well.

(3) We obtained a computer listing of all Aldrich Chemical Company compounds from an EPA/NIH catalog of 170 000 compounds in connectivity-table form and accepted only those with connected C/N skeletons of $3 \leq n \leq 16$ atoms, e.g., compounds like RCOOR′ are catalogued as RCOOH as well as R′OH in the digital format ($z\pi$-lists) described below. This resulted in some 5000 starting materials, which appear in practice to contain all necessary ones. The catalog of course can be expanded. Suppliers could not unfortunately provide computer tapes of all their compounds in usable connectivity-table form.

(4) Hendrickson, J. B. *J. Am. Chem. Soc.* **1977**, *99*, 5439.

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