suggest that in all reports on nitration of reactive aromatics, a description of the method of removal of lower NO_x species should be included. For nitronium salt nitrations the method of Elsenbaumer[8] is recommended whereas with the HNO_3-based reagents NaN_3 may be the scavenger of choice.[24] Note that urea normally is not powerful enough as NO_x scavenger under these circumstances.

Finally, it may be noted that the present catalytic system in principle can be used for other applications, e.g. according to the scheme

$$2ArH + O_2 + 2HX \xrightarrow{NO^+} 2ArX + 2H_2O$$

We are presently investigating the scope and utility of these reactions.

Acknowledgment. I thank Professor Lennart Eberson for stimulating discussions, Dr. Roland L. Elsenbaumer for kindly providing a preprint, and the Swedish Natural Science Research Council for financial support.

Registry No. 1-$BrC_{10}H_7$, 90-11-9; 1-$HC_{10}H_7$, 91-20-3; 1-$CH_3C_{10}H_7$, 90-12-0; 1-$OCH_3C_{10}H_7$, 2216-69-5; $NOBF_4$, 14635-75-7; NO_2, 10102-44-0; N_2O_4, 10544-72-6; 4,4′-dibromo-1,1′-binaphthyl, 49610-35-7; 4,4′-dimethyl-1,1′-binaphthyl, 19224-41-0; 4,4′-dimethoxy-1,1′-binaphthyl, 19817-09-5; 1,2,4-trimethoxybenzene, 135-77-3; 2,2′,4,4′,5,5′-hexamethoxybiphenyl, 14262-07-8.

(24) See, e.g.: Clemens, A. H.; Ridd, J. H.; Sandall, J. B. P. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1227. Fitzpatrick, J.; Meyer, T. A.; O'Neill, M. E.; Williams, D. L. H. *Ibid.* **1984**, 927.

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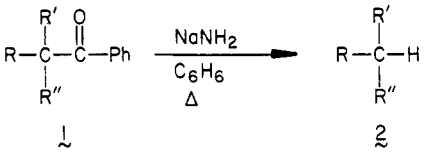
Optically Enriched Alkyltrimethylsilanes by Haller–Bauer Cleavage of Optically Active, Nonenolizable α-Silyl Phenyl Ketones

Summary: Conversion of *l*-menthyl ester **5** to phenyl ketones **7** and Haller–Bauer cleavage (MNH_2, C_6H_6, Δ) delivers the tertiary silanes **8** with 88–92% retention of configuration. The intermediate α-silyl carbanions are therefore generated in chiral condition and protonated almost exclusively on that surface from which benzamide is departing. The cyclic phenyl ketone (−)-**12** also undergoes C–C bond cleavage with excellent (96–98%) levels of configurational retention.

Sir: Optically active C-centered organosilanes[1] are rapidly gaining interest in their own right[2] and as important mechanistic probes.[3] However, progress in this area has been hampered by the unavailability of a *general* synthetic method capable of reliably delivering silanes of known absolute configuration. Herein, we outline a relatively simple protocol capable of realizing this objective.

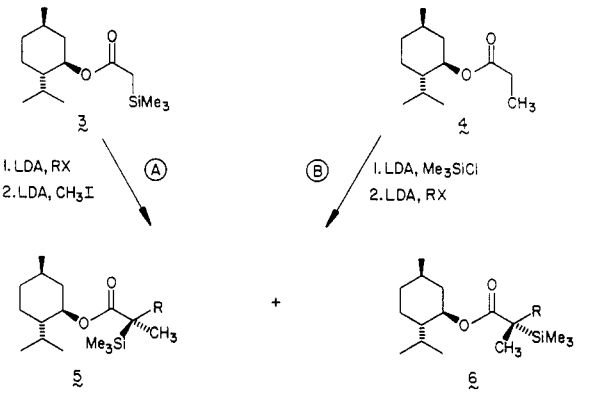
The cleavage of nonenolizable ketones by amide ion (e.g., **1** → **2**, the Haller–Bauer reaction)[4] is recognized to fail if



1 **2**

at least one of the R groups cannot assist in stabilization of the intermediate carbanion. Thus, while the reaction works well when R = phenyl[5] or cyclopropyl,[6] alkyl substitution alone curtails debenzoylation.[4a] Since Me_3Si substituents stabilize carbanions quite effectively,[7] we have proceeded to examine the fate of optically active α-silyl ketones under Haller–Bauer conditions. Relevantly, *bond scission in these systems proceeds invariably with high levels of configurational retention.* These observations, when coupled with a new asymmetric synthesis of func-

Scheme I[a]

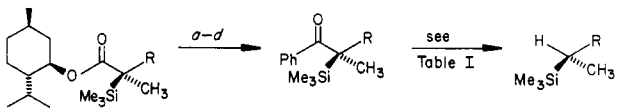


3 **4** **5** **6**

R	route A initial 5:6		route A purified[c] 5	route B initial 5:6		route B purified[c] 6
a, CH_2Ph	55[a]	45	>99% de	31	69	20:80
b, $CH_2CH{=}C(CH_3)_2$	55	45	82% de	38	62	10:90
c, CH_2CH_2Ph	55[b]	45	>99% de	25	75	8:92
d, $(CH_2)_4CH_3$	50	50	89% de	38	62	10:90

[a] Obtained as colorless crystals, mp 68 °C, $[\alpha]^{23}_D$ −56.6° (*c* 1.4, $CHCl_3$). [b] Obtained as colorless crystals, mp 60.5 °C, $[\alpha]^{23}_D$ +3.1° (*c* 2.2, $CHCl_3$). [c] These figures apply to 40–50% mass return of the starting mixture after one chromatographic separation.

Scheme II[a]



5 **7** **8**

[a] (a) Dibal, CH_2Cl_2, 0 °C; (b) Ag_2CO_3, Celite; (c) PhLi; (d) $CrO_3{\cdot}py_2$.

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(7) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467 and references cited therein.

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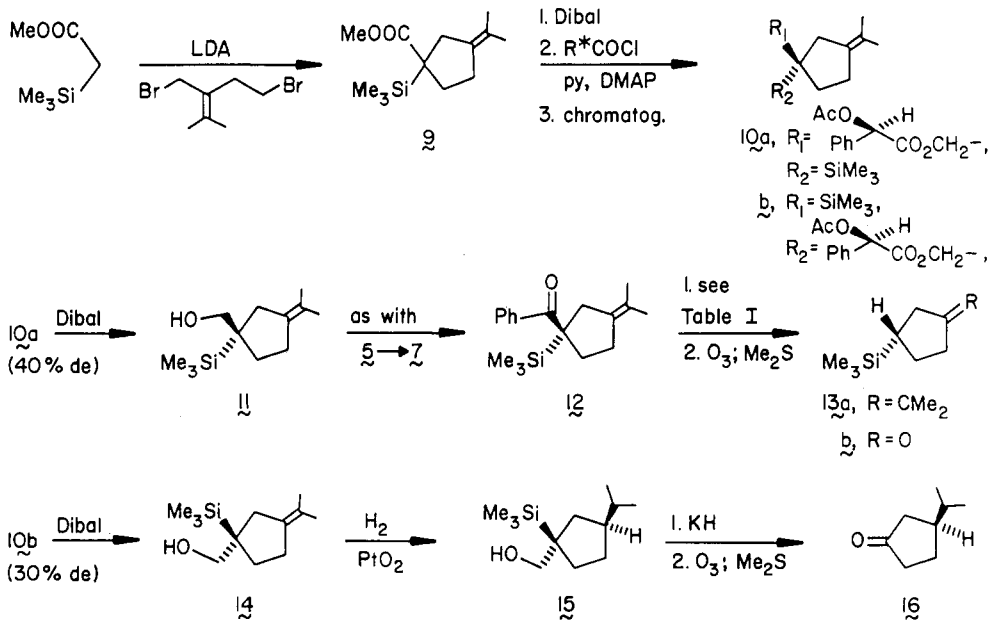
Table I. Haller-Bauer Cleavage of Optically Active 7a-d and 12 (C_6H_6 solution at the reflux temperature)[a]

substr (% ee)	$[\alpha]^{23}_D$ (c, C_6H_6)	base	product ee, %	optical course	
		Open-Chain Series			
7d (89)	+67.7° (7.3)	$NaNH_2$	74	92% ret	8% inv
		KNH_2	68	88% ret	12% inv
7c (99)	+135.3° (2.6)	$NaNH_2$	81	91% ret	9% inv
		KNH_2	77	88% ret	12% inv
7b (46)	+10.1° (2.1)	$NaNH_2$		$[\alpha]^{23}_{365}$ +24.6° (CH_2Cl_2) [b]	
		KNH_2			
7a (99)	+66.1° (4.6)	$NaNH_2$		$[\alpha]^{23}_D$ +31.6° (CCl_4) [b]	
		KNH_2			
		Cyclic Series			
12 (40)	−12.3° (1.3)[c]	$NaNH_2$	38	98% ret	2% inv
		KNH_2	36	96% ret	4% inv

[a] Duplicate experiments at a minimum. [b] Extrapolated values for enantiomerically pure **8b** and **8a** on the basis of consistent 92% and 88% retention levels for $NaNH_2$ and KNH_2, respectively. [c] Recorded in methanol solution.

Scheme III



tionalized tetrasubstituted silanes, satisfy the goals set out above.

Alkylation of the *l*-menthyl ester **3** first with the bromide (iodide) of the targeted substituent R and then with methyl iodide provided diastereomeric mixtures in which **5** was slightly enhanced over **6** (Scheme I). Conversely, C-silylation of propionate **4** and subsequent capture of this enolate by RX delivered **6** in excess. A single chromatographic separation sufficed to give samples of **5** (first component to elute) of high diastereomeric purity. In actuality, **5a** could be efficiently crystallized directly from the reaction mixture. Ester **5c** also proved to be highly crystalline. Since diastereomers **6** eluted last, heightened de was more difficult to achieve on a preparative scale. However, recourse to commercially available *d*-menthol should rectify this matter. The ^1H and ^{13}C NMR spectra of **5** and **6** are sufficiently characteristic to distinguish easily the two series.[8] X-ray analysis of **5a** at <100 °C[9] was therefore utilized to set absolute stereochemistry for all the illustrated examples.

The purified esters **5** were transformed into the benzoyl derivatives **7** via a four-step sequence that skirted the customarily delicate issue of α-desilylation (Scheme II). Table I records the results of the cleavages of enantiomerically enriched **7a–d** with $NaNH_2$ and KNH_2 in refluxing anhydrous benzene solution. Ketones **7c** and **7d** were first examined because the absolute configurations of the corresponding products (**8c**, **8d**) happen to be known.[2c] Simple comparison of $[\alpha]_D$ values in these examples revealed that the intermediate α-silyl carbanions were protonated with 91–92% stereochemical retention when $NaNH_2$ was employed.[10] A slight, though consistent dropoff to the 88% level was noted for those reactions conducted in the presence of potassium amide.[11] When **7a** and **7b** were similarly reacted and the previously observed high levels of stereochemical control were applied to the recorded $[\alpha]_D$s of **8a** and **8b**, optical rotation values for these silanes in optically pure condition could be approximated with a confidence level of ±1° (see Table I). The absolute configurations are in our opinion also accurately assigned.

In order to assess the response of a cyclic system, ester **9** was prepared and reduced with Dibal (Scheme III). Partial resolution into antipodes **11** and **14** was achieved

(8) For example, the α-methyl singlet in **5** invariably appears downfield of that in **6**. The analogous trend is seen for >C*H*O(C=O)—. Characteristically as well, the (CH_3)$_3$Si and >C*H*OCO— carbons of **5** are shielded relative to those in the respective diastereomer.

(9) Gallucci, J. C., private communication.

(10) All products were isolated by solvent distillation through a Vigreux column followed by rigorous purification by preparative GC. Yields ranged from 7% to 35% due principally to competing desilylation and the intrinsic volatility of **8a–d** and **13a** during GC isolation.

(11) Lithium amide in benzene promoted Brook rearrangement of **7** to the silylated enol ether, while potassium *tert*-butoxide in *tert*-butyl alcohol cleanly desilylated these α-silyl ketones.

by chromatographic separation of the *O*-acetylmandelate esters[12] and individual reduction of the purified diastereomers. The indicated absolute configurational assignments to (+)-**11** and (−)-**14** follow from initial chirality transfer in the latter by hydroxyl-directed hydrogenation of the extraannular double bond.[13] Arrival at (−)-**15** was followed by Peterson olefination and ozonolysis to give the known (*S*)-(−)-**16**.[14]

In a companion series of reactions, (+)-**11** was subjected to oxidative phenylation as before. Once (−)-**12** was available, Haller–Bauer cleavage was seen to proceed with outstanding levels of retention (Table I). Direct evidence bearing on the optical purity of (−)-**13a** was gained by ozonolytic cleavage to (−)-**13b**, $[\alpha]^{28}_D$ −68.4° (*c* 0.45, $CHCl_3$), and independent kinetic resolution[15] of 3-(trimethylsilyl)cyclopentene (**17**)[16] by Brown's method.[17] Hydroboration–oxidation of (*S*)-(−)-**17** (34% ee)[2b] according to Larson[16a] gave (*S*)-(−)-**13b**, $[\alpha]^{26}_D$ − 62.3° (*c* 0.75, $CHCl_3$).

In summary, we detail herein a general method for preparing diastereomerically enriched samples of esters **5** and **6**, the phenyl ketones of which have the capacity for generating α-silyl carbanions in chiral condition. Protonation of these reactive species and those in cyclic structures occurs with high retention of configuration in nonpolar benzene solution. This phenomenon should perhaps be regarded as a fundamental chemical process, having earlier played a key role in Cram's development (through use of related processes) of the steric course of electrophilic substitution at saturated carbon.[18] An important and utilitarian route to optically active tertiary silanes such as **8** that possesses reliable stereochemical predictability has now been defined.

Acknowledgment. We express our gratitude to the National Science Foundation for financial support and the Fulbright Commission for a travel grant (to J.P.G.).

Registry No. **3**, 112297-88-8; **4**, 4951-48-8; **5a**, 112297-80-0; **5b**, 112297-81-1; **5c**, 112297-82-2; **5d**, 112297-83-3; **6a**, 112297-84-4; **6b**, 112297-85-5; **6c**, 112297-86-6; **6d**, 112297-87-7; **7a**, 112297-89-9; **7b**, 112297-90-2; **7c**, 112297-91-3; **7d**, 112297-92-4; **8a**, 112297-93-5; **8b**, 112297-94-6; **8c**, 112297-95-7; **8d**, 112297-96-8; **9**, 112297-97-9; **10a**, 112297-98-0; **10b**, 112297-99-1; **11**, 112298-00-7; **12**, 112298-01-8; **13a**, 112298-02-9; **13b**, 112298-03-0; **14**, 112298-04-1; **15**, 112298-05-2; **16**, 93451-75-3; (*S*)-(−)-**17**, 89576-21-6; $BrCH_2Ph$, 100-39-0; $BrCH_2CH{=}C(CH_3)_2$, 870-63-3; $BrCH_2CH_2Ph$, 103-63-9; $Br(CH_2)_4CH_3$, 110-53-2; $MeOCOCH_2SiMe_3$, 2916-76-9; Ph(AcO)CHCOCl, 49845-69-4; 3-bromomethyl-5-bromo-2-methyl-2-pentene, 85221-99-4.

(12) The use of *O*-acetylmandelate esters for resolution was first reported by Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548.

(13) Double irradiation of the Me_3Si singlet at 500 MHz had no effect on the CH_2OH absorption but enhanced the integration of the isopropyl peak by 7.8%.

(14) The (*R*)-(+) enantiomer of **16** has been reported to exhibit $[\alpha]^{20}_D$ +186° ($CHCl_3$): (a) Posner, G. H.; Frye, L. L.; Hulce, M. *Tetrahedron* **1984**, *40*, 1401. (b) Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1904. (c) Naves, Y.-R. *Bull. Soc. Chim. Fr.* **1958**, 1372. For the present sample: $[\alpha]^{23}_D$ −88° (*c* 0.28, $CHCl_3$).

(15) Compare the alternative procedure in ref 2b.

(16) (a) DeJesus, M.; Rosario, O.; Larson, G. L. *J. Organomet. Chem.* **1977**, *132*, 301. (b) Reuter, J. M.; Sinha, A.; Salomon, R. G. *J. Org. Chem.* **1978**, *43*, 2438.

(17) Brown, H. C.; Desai, M. C.; Jadhav, P. K. *J. Org. Chem.* **1982**, *47*, 5065.

(18) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; Chapter IV and relevant references cited therein.

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Stereocontrolled Construction of the Hexahydrobenzofuran Subunit of the Avermectins and the Milbemycins: The Aldol Strategy

Summary: A novel route to the hexahydrobenzofuran subunit (**1**) of the avermectins and the milbemycins has been developed via two successive aldol reactions that proceed with high diastereoselectivity.

Sir: The avermectins[1] and the milbemycins[2] are of considerable current interest because of their unique structures and potent antiparasitic activities, and consequently many papers concerned with their total syntheses have appeared recently.[3,4] We describe herein a stereocontrolled synthesis of the crucial[5] hexahydrobenzofuran subunit **1**[4b,c] in optically active form, which is a versatile synthon for all of the avermectins[1] and the α series of the milbemycins.[2]

Our synthetic strategy for **1** outlined in Scheme I is based on the consideration of these natural products as nonaromatic alicyclic polyketides.[6] The two strategic bond disconnections (C2–C7 and C5–C6) of the retro-aldol type define chiral ketone **4** and achiral aldehyde **5** as building blocks for stereo- and enantioselective construction of **1**:[7] the single chiral center of **4** is designed to induce all of four chiralities essential to **1** via two key aldol reactions.

The kinetic aldol reaction, the first crucial step, of freshly prepared **4**[8] with **5**[9] exhibited good stereoselection

(1) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, R. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216. Springer, J. P.; Arison, B. H.; Hirshfield, J. M.; Hoogsteen, K. *Ibid.* **1981**, *103*, 4221. For a recent review, see: Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.

(2) Mishima, H.; Kurabayashi, M.; Tamura, C.; Sato, S.; Kuwano, H.; Saito, A. *Tetrahedron Lett.* **1975**, 711. Takiguchi, Y.; Mishima, H.; Okuda, M.; Terao, M.; Aoki, A.; Fukuda, R. *J. Antibiot.* **1980**, *33*, 1120. Mishima, H.; Junya, I.; Muramatsu, S.; Ono, M. *Ibid.* **1983**, *36*, 980.

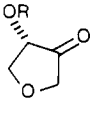
(3) For total syntheses of milbemycin β_3, see: Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenburg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015. Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *Ibid.* **1982**, *104*, 4708. Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1326. Street, S. D. A.; Yeates, C.; Kocienski, P.; Campbell, S. F. *Ibid.* **1985**, 1386, 1388. Barrett, A. G. M.; Carr, R. A. E.; Attwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840.

(4) (a) For syntheses of the spiroacetal subunit of avermectins, see: Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427. Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, *309*. Hirama, M.; Nakamine, T.; Itô, S. *Tetrahedron Lett.* **1986**, *27*, 5281. (b) For syntheses and synthetic studies of the hexahydrobenzofuran subunit, see: Prashad, M.; Fraiser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1556. (c) Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327. Kozikowski, A. P.; MaloneyHuss, K. E. *Tetrahedron Lett.* **1985**, *26*, 5759. Crimmins, M. T.; Lever, J. G. *Ibid.* **1986**, *27*, 291. Hanessian, S.; Beaulieu, P.; Dube, D. *Ibid.* **1986**, *27*, 5071. Barrett, A. G. M.; Capps, N. K. *Ibid.* **1986**, *27*, 5571. Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta* **1986**, *69*, 1273. Ardisson, J.; Ferezou, J. P.; Julia, M.; Pancrazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001. Crimmins, M. T.; Hollis, W. G., Jr.; Lever, J. G. *Ibid.* **1987**, *28*, 3647. (d) Recently a first relay synthesis of avermectin B_{1a} has been reported: Hanessian, S.; Ugolini, A.; Dube, D.; Hodges, P. J.; Andre, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776. Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dube, D.; Andre, C. *Pure Appl. Chem.* **1987**, *59*, 299. See also ref 5.

(5) Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.

(6) Cane, D. E.; Liang, T.-C.; Kaplan, L.; Nallin, M. K.; Schulman, M. D.; Hensens, O. D.; Douglas, A. W.; Albers-Schönberg, G. *J. Am. Chem. Soc.* **1983**, *105*, 4110.

(7) The tetrahydrofuranone **i** would appear to be a more straightforward synthon for the synthesis of **1**. However, this ketone proved to be extremely labile[8] under the conditions of enolate formation, irrespective of the hydroxyl protecting group R.



i

0022-3263/88/1953-0706$01.50/0