Tetrahedron Letters,Vol.25,No.33,pp 3591-3594,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

STEREOSELECTIVE SYNTHESIS OF TRANS-HYDRINDANES BY INTERNAL VINYLSILANE ACYLATION

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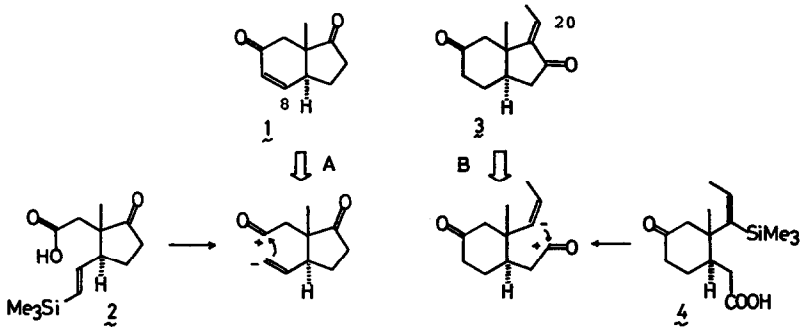
Summary: trans-Hydrindanediones (**1**, **3**, and **15**) have been synthesized in short steps through stereoselective introduction of vinylsilane units onto the cycloalkenones **5** or **10** followed by $AgBF_4$-mediated internal acylation of the vinylsilane moiety.

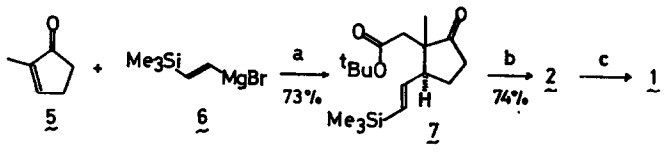
We report here two of our syntheses of functionalized trans-hydrindanes (**1**, **3**, and **15**) that we have developed in conjunction with the projected steroid synthesis.[1] These approaches rely, in common, on an intramolecular acylation reaction of vinylsilanes[2] as the crucial ring forming reaction. The first approach, as shown in Scheme I, utilizes the reaction for the C ring construction, and the second one for the D ring formation.

Scheme I.



The central assumption on which we based our synthesis was that the transformations A and B should be possible via the cyclization of the acid chlorides derived from the acids **2** and **4**, respectively. The virtue of the vinylsilane route is that the ring forming operation leaves an olefin at a specifically desired position, which would be useful for the eventual introduction of substituents at C-8 and C-20. Interests have also been focused on the geometry of the $\Delta^{17,20}$-unsaturation in **3**, since the E-isomer shown should become a viable precursor to the biologically important vitamin D derivatives through C-20 stereoselective introduction of the side

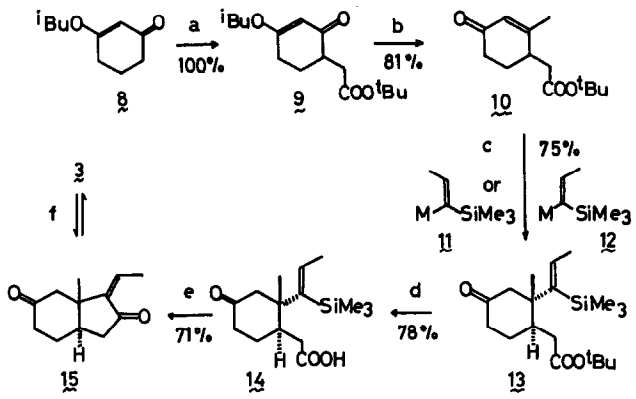
Scheme II.



a: cat. CuI/DMS, THF; $BrCH_2COO^tBu$/HMPA
b: TMSCl/NaI/CH_3CN
c: ref. 7

The synthesis of trans-hydrindane-3,6-dione **1** started from the cyclopentenone **5** (Scheme II). This compound was treated with 1.03 equiv of E-2-trimethylsilylvinylmagnesium bromide (**6**)[4] in THF at -78 to -55 °C for 3.5 h, followed by alkylation with tert-butyl bromoacetate (2.5 equiv) in the presence of 2.5 equiv of HMPA (initially at -78 °C, then 18 h at room temperature) to afford the keto ester **7** in 72% yield.[5] Dealkylative ester hydrolysis with chlorotrimethylsilane (TMSCl)/NaI in acetonirile[6] afforded the acid **2** in 74% yield: The corresponding acid chloride cyclizes to the desired **1** under Lewis acid catalysis.[2,7] Although this route is short and quite efficient, the stereoselectivity with respect to the C,D-ring juncture was only 9:1.[8] We therefore explored the second possibility.

Scheme III.



a: LDA; $BrCH_2COO^tBu$/THF
b: MeMgBr (1.2 eq); 2N HCl
c: **12** (M = MgBr)/CuI
d: TMSCl/NaI/Et_3N/CH_3CN
e: Collidine/DMF/$(COCl)_2$; $AgBF_4$/CH_3NO_2
f: pTsOH

The second route (Scheme III) utilized Stork's sequence[9] to prepare the enone **10**. Thus, the lithium enolate of **8** was alkylated with tert-butyl bromoacetate and then allowed to react with methylmagnesium bromide followed by acidic workup (81% overall). Although the E-1-trimethylsilyl-1-propenyl metal reagent **11** was to be added onto the enone **10** in order for the preparation of **3**, we could not find any conditions to achieve this goal. Both lithium and magnesium reagents (**11**: M = Li or MgBr) obtained from the corresponding Z-bromide (**11**: M = Br)[10] in the presence of a variety of stoichiometric and catalytic copper salts either failed to react with this quite unreactive enone or reacted after isomerization to the Z-reagent **12** to afford the Z-adduct **13** in stead of **3**. The Z-Grignard reagent **12** (M = MgBr),[10] on the other hand, underwent clean addition in the presence of CuI and excess dimethylsulfide

(DMS) to afford **13** (75%) with at least 97% stereoselectivity.[11] The stereoselection with respect to C-14 (steroid numbering) must be the desired one in the light of literature precedents.[12] The dealkylative conversion of the ester to the acid **14** was achieved in 78% yield as before. The crucial cyclization of **14** was performed first by conversion to the acid chloride in the presence of collidine, followed by treatment of the crude acid chloride with 2.5 equiv of $AgBF_4$ in nitromethane. The reaction was stereospecific, giving the Z-enone **15** in 71% yield as a solid (mp 49--50 °C). The cyclization reaction performed with $TiCl_4$ initially gave **15** in high yield, which rapidly isomerized to a readily separable 1:1 mixture of **3** and **15**.[12] Since quantitative conversion of **15** to such an isomeric mixture can be achieved smoothly under mild acidic conditions,[14] the desired **3** could also be obtained pure after a few chromatography/isomerization cycles.

The experimental procedure for the preparation of **15** follows:[15]

The Keto Ester 13. A mixture of CuI (11.9 g, 62.2 mmol), DMS (9.60 ml, 131 mmol) in 50 ml of dry THF under nitrogen was cooled to -70 °C and the Grignard reagent **12** (M = MgBr) (0.43 M THF solution, 128 mmol) was added during 25 min. After stirring for 15 min at -60 °C, the mixture was cooled to -70 °, and the enone **10** (7.80 g, 34.8 mmol) in 20 ml of THF was added during 7 min. After 70 min at -65 °C, the mixture was poured into a stirred solution of NH_4Cl. Extractive workup followed by chromatography gave **13** (8.88 g, 75%).

The Acid 14. A mixture of the keto ester **13** (1.38 g, 4.07 mmol), NaI (2.45 g, 16.3 mmol), Et_3N (2.40 ml, 17.2 mmol), and TMSCl (2.00 ml, 15.8 mmol) in 7 ml of acetonitrile was heated at 70 °C for 20 min. After extracted workup was obtained the title acid (0.90 g, 78%).

The Hydrindanedione 15. To a mixture of the acid **14** (0.19 g, 0.67 mmol), DMF (3 micro l), collidine (0.11 ml, 0.81 mmol) in 0.8 ml of methylene chloride at 0 °C was added oxallyl chloride (70.4 micro l, 0.87 mmol). After 2.5 h, volatile material was removed in vacuo and the dark residue was diluted with hexane and filtered. The filtrate was concentrated and then added to $AgBF_4$ (0.33 g, 1.71 mmol) in 1.4 ml of nitromethane at 0 °C. After 1.5 h at room temperature, the product was isolated by usual aqueous workup to obtain 93.2 mg (71%) of **15**.

Acknowledgment. Financial support by the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Research) is deeply acknowledged.

References and Notes

(1) Contents of this paper have been orally presented at the Annual Meeting of the Chemical Society of Japan, April 1983, Osaka, and also described in a thesis by K. F.: Tokyo Institute of Technology, March, 1983.

(2) (a) Burke, S. D.; Murtiashaw, C. W.; Dike, M. S.; Smith Strickland, S. M.; Saunders, J. O. J. Org. Chem. **1981**, 46, 2400. (b) Mikami, K.; Kishi, N.; Nakai, T. Tetrahedron Lett. **1983**, 24, 795. (c) Nakamura, E.; Fukuzaki, K.; Kuwajima, I. J. Chem. Soc., Chem. Commun. **1983**, 499.

(3) Schmuff, N. R.; Trost, B. M. J. Org. Chem. **1983**, 48, 1404.

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(5) Cf. Ito, Y.; Nakatsuka, M.; Saegusa, T. J. Am. Chem. Soc. **1981**, 103, 476. We thank Prof. Y. Ito for the details of the experimental procedure for the alkylation reaction.

(6) Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Mahotra, R. J. Org. Chem. **1979**, 44, 1247.

(7) An essentially identical approach has just been reported: Denmark, S. E.; Germanas, J. P. Tetrahedron Lett. **1984**, 25, 1231.

(8) (a) In systems closely related to the present one, some[5,7] reported a stereoselectivity of the alkylation as high as 95%, while others[8b] reported only moderate selection. (b) Cf. Oppolzer, W.; Battig, K.; Petrzilka, M. Helv. Chim. Acta **1978**, 61, 1945. Nicolaou, K. C.; Barnette, W. E.; Ma, P. J. Org. Chem. **1980**, 45, 1463.

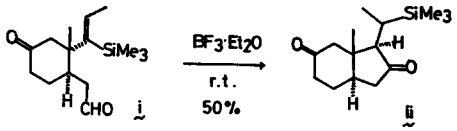
(9) Stork, G.; Danheiser, R. L. J. Org. Chem. **1973**, 38, 1775. **8**: available in 90% yield from cyclohexanedione: Gannon, W. F.; House, H. O. Org. Syn. **1973**, Coll. Vol. 5, 539.

(10) E-1-Bromo-1-trimethylsilylpropene (**12**: M = Br; 6.80, q, J = 8 Hz) was prepared by a standard hydroalumination/bromination sequence with a 97% selectivity: Zweifel, G.; Lewis, W. J. Org. Chem. **1978**, 43, 2739. The Z-isomer **11** (M = Br; 6.32, q, J = 6 Hz) of 99% isomeric purity was made by isomerizing **12** by slow distillation at ca. 70 °C (X 2). This isomerization reaction seems specific for this particular substrate.

(11) The degree of the stereoselection was determined by capillary GLC analysis (PEG-20M, 20 m, 170 °C). A minor isomeric peak (ca. 3%) could either be the E-geometrical or cis-stereoisomer.

(12) Wege, P. M.; Clark, R. D.; Heathcock, C. H. J. Org. Chem. **1976**, 41, 3144. Blumenkopf, T. A.; Heathcock, C. H. J. Am. Chem. Soc. **1983**, 105, 2354.

(13) Interestingly, the silyl group was retained in a related $BF_3 \cdot Et_2O$ catalyzed reaction of the aldehyde i, to give a product, to which the structure ii was tentatively assigned: unpublished result by Y. Horiguchi.



(14) (a) Cf. Koreeda, M; Tanaka, Y.; Schwartz, A. J. Org. Chem. **1980**, 45, 1172. (b) This must be the reason for the loss of stereospecificity in cases reported by Nakai.[2b]

(15) Physical properties of the key compounds are listed below:

7: IR (neat) 1735, 1720 cm^{-1}; ^1H NMR (CCl_4) 0.98 (s, Me); MS (20 eV) m/e 254 ($M^+ - C_4H_8$), 73 (100%).

10: IR (neat) 1725, 1665, 1625; ^1H NMR (CCl_4) 1.42 (s, 9 H), 1.90 (br s, 3 H), 1.98--2.92 (m, 7 H), 5.62 (q, 1 H, J = 2 Hz). Anal. $C_{13}H_{20}O_3$: (C, H).

13: Mp 62-63 °C; IR (CCl_4) 1720, 1715; ^1H NMR (CCl_4) 0.30 (s, 9 H), 0.86 (s, 3 H), 1.38 (s, 9 H), 1.58--2.90 (m, 9 H), 1.76 (d, 3 H, J = 6 Hz), 5.89 (q, 1 H. J = 6 Hz). Anal. $C_{19}H_{34}O_3Si$: (C, H).

14: Mp 140--142 °C; IR ($CHCl_3$) 3500--2400, 1705; ^1H NMR ($CDCl_3$) 0.47 (s, 9 H), 1.06 (s, 3 H), 1.96 (d, 3 H, J = 6 Hz), 2.12--3.16 (m, 9 H), 6.14 (q, 1 H, J = 6 Hz), 10.22 (br s, 1 H). Anal. $C_{15}H_{26}O_3Si$: (C, H).

15: Mp 49--50 °C; IR (CCl_4) 1720, 1705, 1645; ^1H NMR (CCl_4) 0.87 (s, 3 H), 1.73--2.60 (m, 14 H), 2.00 (d, 3 H, J = 7 Hz), 5.48 (q, 1 H, J = 7 Hz). Anal. $C_{12}H_{16}O_2$: (C, H).

(Received in Japan 20 April 1984)