Pergamon

Tetrahedron, Vol. 53, No. 32, pp. 11211-11222, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00378-5

A Titanium (IV) Mediated One-Pot Double Condensation Synthesis of 5,6-Dihydro-4*H*-Pyran-4-ones ‡

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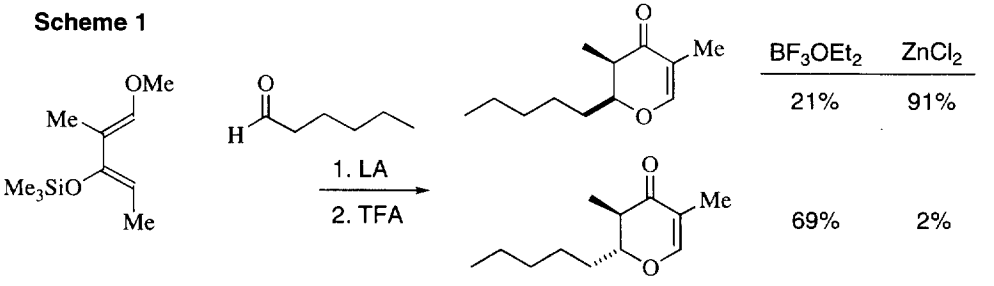
Abstract: An alternative method for the synthesis of 2-amino-5,6-dihydro-4*H*-pyran-4-ones and 5,6-dihydro-4*H*-pyran-4-ones is described. This preparation makes use of the condensation of titanium enolates derived from β-hydroxy ketones with phosgene iminium chloride or trimethylorthoformate, respectively. The *in situ* formation of the necessary titanium complex from an aldol condensation using simple ketone and aldehyde precursors makes for a one-pot double condensation synthesis of the desired dihydropyrones. © 1997 Elsevier Science Ltd.

The 5,6-dihydro-4*H*-pyran-4-one ring system occupies a central position in the structure of a diverse array of natural products.[1] In addition, this useful template provides a rich source of functionality for the synthesis of a variety of structural types including carbohydrates. polypropionates, and other related ring systems.[2] The Lewis acid catalyzed Diels-Alder reaction of silyloxydienes and aldehydes pioneered and developed by Danishefsky and coworkers provides an expeditious route to the δ-pyrone ring.[3] In most cases, the stereochemical outcome of these reactions is controlled through the proper choice of Lewis acid (Scheme 1). Moreover, the use of chiral catalysts and substrates has resulted in an asymmetric version of this process.[4] This Diels-Alder reaction is also successful with ketone dienophiles, generating the corresponding 6, 6-disubstituted dihydropyrone.[5]

Scheme 1



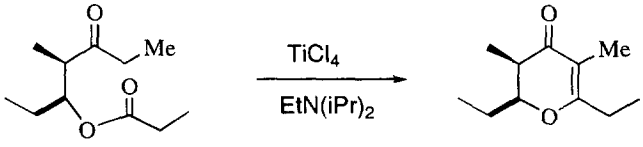
BF_3OEt_2	$ZnCl_2$
21%	91%
69%	2%

An attractive alternative synthesis of the dihydropyrone ring, recently described by Oppolzer, involves a titanium mediated cyclization of a β-acyloxyketone intermediate (Scheme 2).[6,1] The β-acyloxyketones

‡Dedicated to Professor Samuel J. Danishefsky in celebration of his love for the art of organic synthesis.

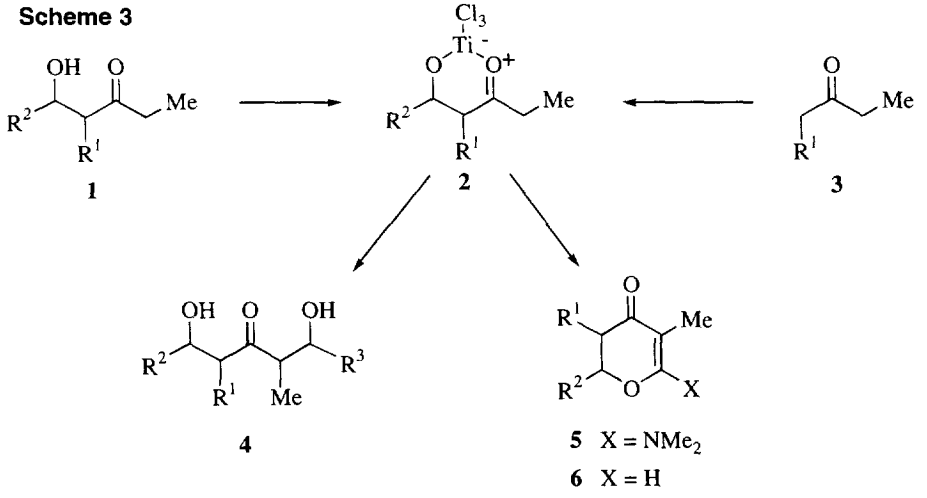
required for this process are readily available in optically pure or racemic form through the application of standard aldol methodology. The desired dihydropyrones are produced in good yield with complete retention of the stereochemical integrity present in the β-acyloxyketone starting material.

Scheme 2



We recently described the condensation of aldehydes with enolates derived from titanium (IV) complexes **2** of β-hydroxyketones **1** producing aldol products of the general structure **4** (Scheme 3).[7] Moderate to excellent sterochemical control was obtained in these condensations depending on the initial ketone stereochemistry and substitution. The possibility that such enolates derived from **2** could be induced to react with electrophiles of higher oxidation states prompted us to consider a complimentary route to the 5, 6-dihydropyrone ring system represented by **5** and **6**. Moreover, since titanium complexes such as **2** are routinely generated via a titanium mediated aldol condensation from **3**,[8] we were intrigued by the possibility that such a dihydropyrone synthesis could be accomplished in one pot via two consecutive condensation reactions starting from simple ketone and aldehyde intermediates. In this paper, we report the successful application of this strategy to the preparation of both 2-amino-5, 6-dihyro-4*H*-pyran-4-ones (**5**) and 5, 6-dihydro-4*H*-pyran-4-ones (**6**).

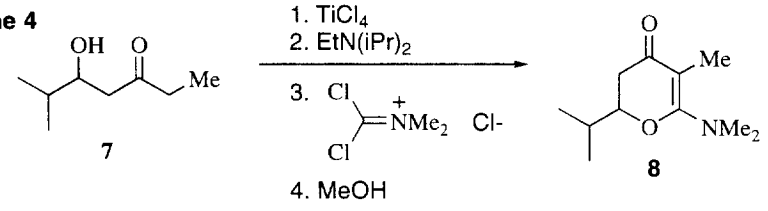
Scheme 3



We initially examined the reaction of phosgene iminium chloride with the enolate generated from the titanium (IV) complex of β-hydroxyketone **7** (**1**: R^1 = H, R^2 = *i*-propyl) (Scheme 4). The reaction of this phosgeniminium salt with enolates derived from Lewis Acid complexes of 2'-hydroxypropiophenones and

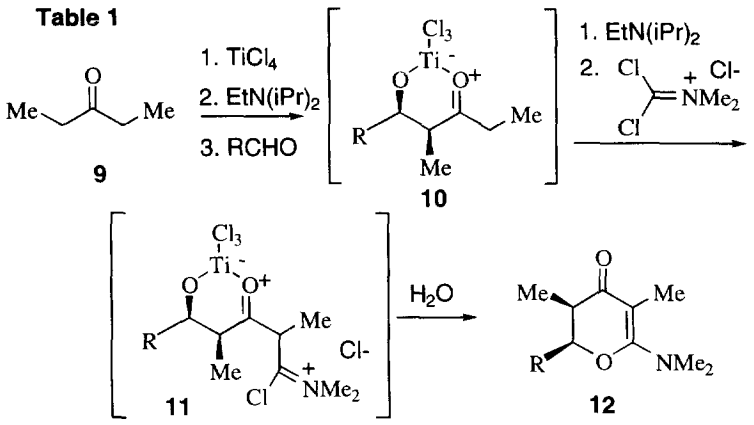
related β-diketones has successfully been applied to a high yielding synthesis of 2-aminochromones and 2-aminopyrones, respectively.[9] Treatment of a methylene chloride solution of **7** with $TiCl_4$ (-78 to 0 °C) and Hunig's base (-78 to 0 °C) (deep red solution) followed by phosgene iminium chloride (0 °C to rt) afforded after methanol quench a 30% yield of **8**.[10] The modest yield of this transformation was similar to that obtained in the related aldol condensation of **7** with isobutyraldehyde and may be associated with the absence of an R^1 substituent.[7]

Scheme 4

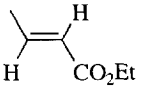


We next chose to explore the reactions of a series of β-hydroxyketone substrates incorporating a R^1 methyl group. Furthermore, the complexity of these reactions was intentionally increased by the decision to utilize the titanium (IV) complexes generated *in situ* from the titanium mediated aldol condensation of simple ketone and aldehyde starting materials as the substrates for enolization. In the examples shown in Table 1, the titanium tetrachloride / Hunig's base generated enolate of 3-pentanone (**9**) was allowed to react with a series of aldehydes at 0 °C. The resultant intermediate titanium aldolate **10** was recooled to -78 °C and subjected to a *second enolization* of the ketone with Hunig's base prior to reaction with the phosgene iminium chloride. In general, after an aqueous quench of the newly formed complexes **11**, the 2-amino-5, 6-dihydropyrones **12** were isolated in 55-75% yields. Acetaldehyde and propionaldehyde proved to be outliers affording 11% and 16% yields of their respective dihydropyrones. In the former case, this proved to be at least in part due to the poor performance of the intitial titanium mediated aldol reaction of acetaldehyde with 3-pentanone. In the example with propionaldehyde, a 51% recovery of the initial aldol product derived from **10d** was obtained. In most cases, the 5, 6-syn products were isolated exclusively, reflecting the syn preference of the initial aldol condensation ($J_{5H\text{-}6H}$ = 2.5-3.2 Hz).[8b] However, with pivalaldehyde, a 3:1 syn / anti mixture of dihydropyrones **12b** was produced. In a more complex example affording dihyropyrone **12f** in 75% yield, the process appeared unaffected by the presence of a carboxylic ester. The addition of two eq of Hunig's base appears to be necessary before introduction of the phosgene iminium chloride for optimum production of the 2-amino-dihydropyrone. In the case of isobutyraldehyde, an attempt using 1.1 eq of base resulted in a reduced 20% yield of **12a**. A similar requirement was noted with the reaction of phosgeniminium salts with β-diketones and appears to be related to the lower pK_a associated with the product complex **11** relative to the that of the pre-enolate complex **10**.[9]

Table 1



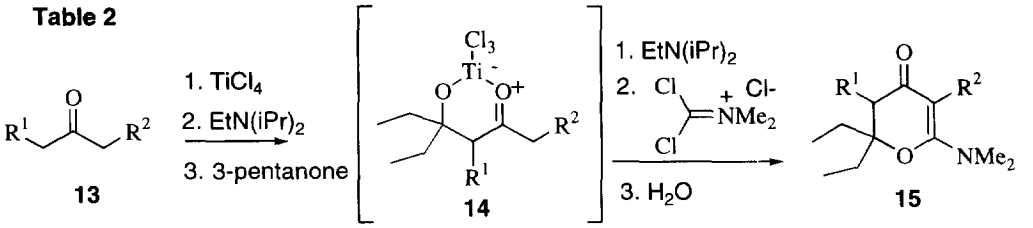
9 **10** **11** **12**

entry	R	% Yield **12**
a	-$CH(CH_3)_2$	65
b	-tBu	62 (3:1 syn/anti)
c	-CH_3	11
d	-CH_2CH_3	16
e	-Ph	56
f		75

This strategy was also applied to the synthesis of a series of 6, 6-disubstituted-2-amino-5, 6-dihydropyrones through the utilization of a *ketone* as the electrophile in the initial aldol condensation (Table 2). The overall yields of the dihydropyrones from this one pot / double condensation process ranged from 48-68%. For comparison, the phosgeniminium salt reaction producing **15b** was also run starting with the purified β-hydroxyketone derived from **14b**. For this example, the overall efficiency of the one pot reaction proved similar to that of the two step procedure (47% vs. 48% yields, respectively). In the case of the reaction beginning with the enolization of 2-butanone (entry d), a 2:1 mixture of regioisomeric dihydropyrones was obtained (48% combined yield).

The synthesis of C-2 unsubstituted dihydropyrones using this strategy made use of trimethylorthoformate as the electrophile for the second condensation step. In each example, the intermediate titanium aldolate was treated with 1 eq of Hunig's base, followed by additional $TiCl_4$ after introduction of the orthoformate.[8a] The corresponding dimethylacetals **19** were isolated in yields of 56 to 76 % (Table 3). Cyclization of **19a-d** with formic acid (rt) afforded the 5, 6-dihydro-4*H*-pyran-4-ones **20a-d** in 77-97 %

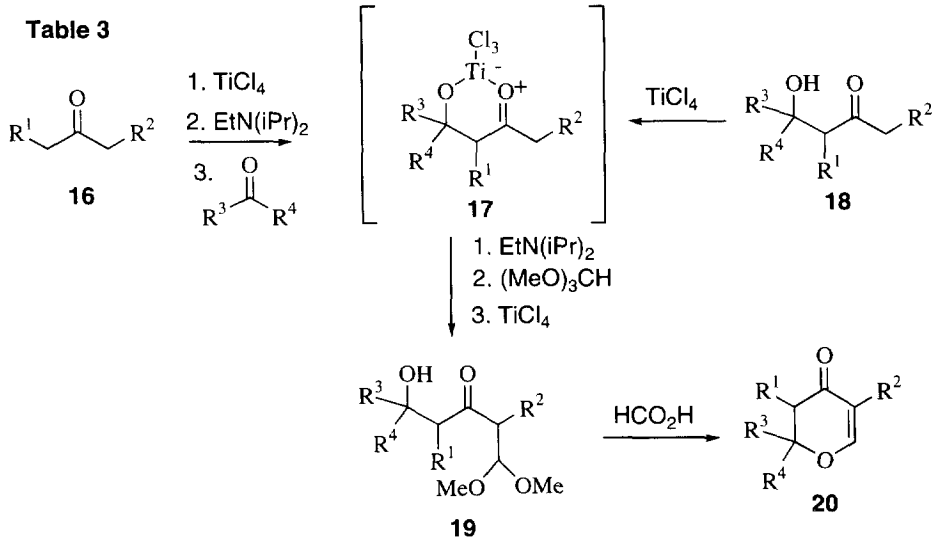
Table 2



13 14 15

entry	R^1	R^2	% Yield **15**
a	-H	$-CH(CH_3)Ph$	68
b	-H	$-CH(CH_3)_2$	47
c	$-CH_3$	$-CH_3$	59
d	-H	$-CH_3$	31
	$-CH_3$	-H	17

Table 3



16 17 18 19 20

entry	R^1	R^2	R^3	R^4	% **19**	% **20**
a	-H	$-CH(CH_3)_2$	-Et	-Et	56	95
b	$-CH_3$	$-CH_3$	-H	$-CH(CH_3)_2$	55	77
c	-H	$-CH(CH_3)Ph$	-Et	-Et	63	97
d	-H	$-CH(CH_3)Ph$	$-(CH_2)_2$-p-F-Ph	$-(CH_2)_2$-p-F-Ph	76	98

yields. For comparison, two cases (entries a and b) were performed starting with the corresponding β-hydroxyketone **18**, producing the dihydropyrones **20a** and **20b** in 83% and 42% yields, respectively. In a separate experiment, β-hydroxyketone **18a** was converted directly to **20a** in 83% overall yield.

In summary, an alternative method for the synthesis of 5, 6-dihydro-4*H*-pyran-4-ones starting from a β-hydroxyketone template has been presented. Moreover, this strategy complements other methodology by allowing for the generation of 2-amino-dihydropyrones in good yield. Since optically pure β-hydroxyketones are widely available utilizing a variety of asymmetric aldol methods, this technique should be applicable to the enantioselective synthesis of many classes of substituted dihydropyrones.[7] Finally, for the synthesis of 5, 6-syn or unsubstituted substrates, the titanium mediated one-pot double condensation reaction provides an efficient synthesis of the 5, 6-dihydropyrone starting with simple ketone and aldehyde starting materials.

Experimental Section

5,6-Dihydro-2-dimethylamino-3-methyl-6-(1-methylethyl)-4*H*-pyran-4-one (8). To a solution of 220.1 mg (1.53 mmol) of hydroxy ketone **1** in 6.1 mL of dry CH_2Cl_2 at -78 °C was added 0.18 mL (1.68 mmol) of $TiCl_4$. The yellow slurry was warmed to 0 °C for 30 min, the cream colored slurry was cooled to -78 °C, and 0.82 mL (4.73 mmol) of *i*-Pr_2NEt was slowly added. The orange slurry was warmed to 0 °C for 30 min and 322 mg (1.98 mmol) of phosgene iminium chloride was added in one portion to the deep red enolate solution. The red-orange mixture was stirred at 0 °C for 4 h 45 min and was quenched by the addition of 6 mL of MeOH. The resulting yellow-orange solution was stirred at rt for 1 h and was neutralized by the slow addition of 3 mL of satd aq $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 and washed with H_2O and brine. The aqueous washes were reextracted once with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The crude material (184 mg) was chromatographed on silica gel, eluting with 20:20:1 CH_2Cl_2-EtOAc-MeOH followed by 10:10:1 CH_2Cl_2-EtOAc-MeOH to afford 90.2 mg (30%) of **8**. ^{1}H NMR ($CDCl_3$) δ 3.90 (ddd, J = 12.3, 6.8, 4.2 Hz, 1), 2.95 (s, 6), 2.43, 2.32 (ABX, J_{AB} = 16.3, J_{AX} = 12.3, J_{BX} = 4.2 Hz, 2), 1.92 (oct, J = 6.8 Hz, 1), 1.79 (s, 3), 1.03 (d, J = 6.7 Hz, 3), 0.97 (d, J= 6.8 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 191.3, 168.7, 89.3, 81.5, 39.4, 38.7, 31.8, 18.2, 18.1, 11.0.

5R*,6S*-3,5-Dimethyl-2-dimethylamino-6-(1-methylethyl)-5,6-dihydro-4*H*-pyran-4-one (12a). A solution of 3-pentanone (0.505 mL, 5.0 mmole) in 15 mL of CH_2Cl_2 at -78°C was treated with $TiCl_4$ in CH_2Cl_2 (5.25 mL, 5.25 mmole). After 20 min, the yellow suspension was treated with N,N diisopropylethyl amine (0.958 mL, 5.5 mmole) and stirred for 30 min at -78°C. The red enolate was treated with isobutyraldehyde (0.545 mL, 6.0 mmole), stirred for 30 min at 0°C, and recooled to -78°C. The mixture was treated with N,N

diisopropylethyl amine (1.83 mL, 10.5 mmole) and stirred for 30 min at 0°C. The newly formed dark red enolate was treated with phosgene iminium chloride (1.06 g, 6.5 mmole) and the reaction was stirred for 2 h at 0°C. The mixture was quenched with 50 mL of 50% saturated ammonium chloride and stirred vigorously for 1 h. The aqueous layer was extracted with 2 x 20 mL of CH_2Cl_2. The combined organics were washed with 25 mL of saturated $NaHCO_3$ and the aqueous wash was reextracted 20 mL of CH_2Cl_2. The combined organics were dried over K_2CO_3 and were concentrated *in vacuo* to an amber oil. The crude material was chromatographed over 50 g of silica gel (230-400 mesh), eluting with 3% MeOH/ CH_2Cl_2 to give 691 mg (65%) of **12a** as a pale oil which crystallized on standing; Mp: 105-106 °C; ^{1}H NMR ($CDCl_3$): δ 0.81 (d, *J* = 6.8 Hz, 3), 0.96 (d, *J* = 7.4 Hz, 3), 1.03 (d, *J* = 6.5 Hz, 3), 1.72 (s, 3), 1.96 (m, 1), 2.29 (dq, J = 2.7, 7.3 Hz, 1), 2.92 (s, 6), 3.65 (dd, *J* = 2.7, 10.3 Hz, 1); ^{13}C NMR ($CDCl_3$): δ 9. 5, 10.4, 17.8, 19.6, 28.3, 39.5, 41.2, 84.6, 87.7, 168.2, 196.3; R_f 0.28, 5% MeOH/CH_2Cl_2; IR: 2926, 1567, 1474, 1456 cm^{-1}. Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02 N, 6.63. Found: C, 68.39; H, 9.78; N, 6.65.

5R*,6S*-6-t-butyl-3,5-dimethyl-2-dimethylamino-5,6-dihydro-4*H*-pyran-4-one (**12b**) was prepared according to the procedure described for **12a** starting with 3-pentanone (0.505 mL, 5.0 mmole) and 2,2,2-trimethylacetaldehyde (0.649 mL, 6.0 mmole). Yield of **12b**, 702 mg (62%) as a 3:1 mixture of syn/anti stereoisomers; ^{1}H NMR ($CDCl_3$): δ 1.02 (s, 9), 1.08 (d, *J* = 7.3 Hz, 3), 1.74 (s, 3), 2.40 (dq, *J* = 2.5, 7.3 Hz, 1), 2.94 (s, 6), 3.83 (d, *J* = 2.5 Hz, 1); ^{13}C NMR ($CDCl_3$): δ 11.0, 11.7, 27.1, 34.3, 39.5, 42.2, 85.7, 87.4, 89.0, 168.7, 196.6; R_f 0.32, 5% MeOH/CH_2Cl_2; 2959, 1568, 1396 cm^{-1}. HRMS: Calcd for $C_{13}H_{23}NO_2$: 225.1729. Found: 225.1729.

5R*,6S*-2-Dimethylamino-3,5,6-trimethyl-5,6-dihydro-4*H*-pyran-4-one (**12c**) was prepared according to the procedure described for **12a** starting with 3-pentanone (0.505 mL, 5.0 mmole) and acetaldehyde (0.339 mL, 6.0 mmole). Yield of **12c**, 102 mg (11%) as a pale yellow oil; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, *J* = 6.9 Hz, 3), 1.29 (d, *J* = 6.5 Hz, 3), 1.76 (s, 3), 2.20 (dq, *J* = 3, 7.3 Hz, 1), 2.92 (s, 6), 4.39 (dq, *J* = 3, 6.6 Hz, 1); IR: 3407, 2939, 1634, 1558, 1455 cm^{-1}. HRMS: Calcd for $C_{10}H_{17}NO_2$: 183.1259. Found: 183.1260.

5R*,6S*-3,5-Dimethyl-2-dimethylamino-6-ethyl-5,6-dihydro-4*H*-pyran-4-one (**12d**) was prepared according to the procedure described for **12a** starting with 3-pentanone (0.505 mL, 5.0 mmole) and propionaldehyde (0.433 mL, 6.0 mmole). Yield of **12d**, 156 mg (16%) as a colorless oil; ^{1}H NMR ($CDCl_3$): δ 0.96 (t, *J* = 7.5 Hz), 1.00 (d, *J* = 7.3 Hz), 1.46-1.57 (m, 2), 1.72 (s, 3), 1.69-1.83 (m, 2), 2.20 (dq, *J* = 3, 7.35 Hz, 1), 2.91 (s, 6), 4.07 (m, 1); ^{13}C NMR ($CDCl_3$): δ 9.6, 10.0, 11.0, 23.4, 39.4, 42.6, 80.5, 87.9, 168.1, 196.0; R_f 0.13, 5% MeOH/CH_2Cl_2; IR: 2969, 1564, 1398, 1379 cm^{-1}. HRMS: Calcd for $C_{11}H_{19}NO_2$: 197.1416. Found: 197.1418.

5R*,6S*-3,5-Dimethyl-2-dimethylamino-6-phenyl-5,6-dihydro-4*H*-pyran-4-one (**12e**) was prepared according to the procedure described for **12a** starting with 3-pentanone (0.505 mL, 5.0 mmole) and

benzaldehyde (0.610 mL, 6.0 mmole). Yield of **12e**, 690 mg (56%) as a pale yellow crystalline solid; Mp: 122-123°C; ^{1}H NMR ($CDCl_3$): δ 0.87 (d, *J* = 7.3 Hz, 3), 1.84 (s, 1), 2.50 (dq, *J* = 3, 7.4 Hz, 1), 3.01 (s, 6), 5.37 (d, *J* = 3 Hz, 1), 7.35 (m, 5); ^{13}C NMR ($CDCl_3$): δ 9.8, 11.1, 39.7, 45.3, 79.8, 88.1, 125.4, 127.7, 128.5, 137.2, 167.7, 195.9; R_f 0.32, 5% MeOH/CH_2Cl_2; IR: 2925, 1561, 1396 cm^{-1}. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.55; H, 7.64; N, 5.78.

5R*,6S*-5,6-Dihydro-3,5-dimethyl-2-dimethylamino-6-(3-ethoxycarbonyl-1*E*-propenyl)-4*H*-pyran-4-one (12f) was prepared according to the procedure described for **12a** starting with 3-pentanone (578 mg, 6.71 mmol) and ethyl 4-oxo-2*E*-butenoate (903.4 mg, 7.05 mmol). Yield of **12f**, 1.342 g (75%); ^{1}H NMR ($CDCl_3$) δ 6.88 (dd, *J* = 15.8, 4.0 Hz, 1), 6.16 (dd, *J* = 15.8, 2.0 Hz, 1), 4.93 (ddd, *J* = 4.0, 3.2, 2.0 Hz, 1), 4.24 (q, *J* = 7.2 Hz, 2), 2.99 (s, 6), 2.41 (qd, *J* = 7.4, 3.2 Hz, 1), 1.80 (s, 3), 1.33 (t, *J* = 7.2 Hz, 3), 1.03 (d, *J* = 7.4 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 194.0, 166.4, 165.3, 141.5, 121.9, 87.5, 76.7, 60.3, 42.4, 39.2, 13.8, 10.5, 9.8; IR 1721, 1567 cm^{-1}. HRMS: Calcd for $C_{14}H_{21}NO_4$: 267.1470. Found: 267.1465.

6,6-Diethyl-5,6-dihydro-2-dimethylamino-3-(1-phenyl)ethyl-4*H*-pyran-4-one (15a). To a solution of 2.459 g (15.16 mmol) of 4-phenyl-2-pentanone in 60 mL of dry CH_2Cl_2 at -78 °C was added 1.75 mL (15.92 mmol) of $TiCl_4$ followed by 2.90 mL (16.67 mmol) of *i*-Pr_2NEt. The deep red solution was stirred a -78 °C for 30 min. whereupon 1.75 mL (16.67 mmol) of 3-pentanone was added. The mixture was then warmed to 0 °C for 30 min, cooled to -78 °C, and 5.54 mL of *i*-Pr_2NEt was slowly added. The reaction mixture was stirred at 0 °C for 30 min, recooled to -78 °C, and 3.69 g (22.7 mmol) of phosgene iminium chloride was added in one portion. The reaction mixture was stirred at 0 °C for 1.5 h and diluted with 60 mL of H_2O. The resulting yellow mixture was stirred vigorously for 2 h and was then extracted with CH_2Cl_2. The extract was washed with half satd aq $NaHCO_3$ and brine. The aqueous washes were rextracted once with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$ and concentrated to 4.92 g of a yellow oil. The crude material was chromatographed over silica gel, eluting with 3:2, 1:1, and 1:2 hexanes-Et_2O to afford 3.09 g (68%) of **15a** and 772 mg (21%) of the aldol product derived from **14a**. **15a**: ^{1}H NMR ($CDCl_3$) δ 7.32-7.20 (m, 4), 7.13-7.08 (m, 1), 3.77 (q, *J* = 7.2 Hz, 1), 2.80 (s, 6), 2.46, 2.39 (ABq, *J* = 16.2 Hz, 2), 1.89-1.80, 1.65-1.52 (m, 4), 1.68 (d, *J* = 7.2 Hz, 3), 0.90 (t, *J* = 7.5 Hz, 3), 0.87 (t, *J* = 7.4 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 189.7, 167.8, 146.3, 127.7, 127.5, 125.1, 97.1, 82.5, 44.3, 40.4, 37.3, 28.0, 26.9, 19.7, 8.0, 7.8 ppm; IR 1629, 1551, 1447, 1387 cm^{-1}. HRMS: Calcd for $C_{19}H_{27}NO_2$: 301.2042. Found: 301.2064.

6,6-Diethyl-5,6-dihydro-2-dimethylamino-3-(1-methyl)ethyl-4*H*-pyran-4-one (15b). A solution of 4-methyl-2-pentanone (0.625 mL, 5 mmole) in 15 mL of dry CH_2Cl_2 at -78°C, was treated with $TiCl_4$ in CH_2Cl_2 (5.25 mL, 5.25 mmole). After 15 min, the yellow solution was treated with *i*-Pr_2NEt (0.958 mL, 5.5 mmole), and the resulting deep red solution was stirred 30 min at -78°C. The mixture was treated with 3-pentanone

(0.606 mL, 6.0 mmole), warmed to 0°C, and stirred for 1 h. The amber solution was cooled to -78°C, treated with *i*-Pr_2NEt (1.83 mL, 10.5 mmole), and the solution was warmed to 0°C. After 30 min, the mixture was treated phosgene iminium chloride (1.06 g, 6.5 mmole) and stirred for 1.5 h at 0°C. The mixture was quenched with 40 mL of H_2O and vigorously stirred. The aqueous layer was extracted with 2 x 20 mL of CH_2Cl_2, and the combined organics were washed with 40 mL of saturated $NaHCO_3$. The organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The crude material was chromatographed over 50 g of silica gel (230-400 mesh), eluting with 30% EtOAc/hexanes followed by 50% EtOAc/hexanes to afford 565 mg (47%) **15b** as a white crystalline solid along with 216 mg (23%) the aldol product derived from **14b**. **15b**: Mp: 65-66°C; ^{1}H NMR ($CDCl_3$): δ 0.86 (t, *J* = 7.5 Hz, 6), 1.27 (d, *J* = 6.9 Hz, 6), 1.68 (m, 4), 2.33 (s, 2), 2.39 (m, 1), 2.86 (s, 6); ^{13}C NMR ($CDCl_3$): δ 7.9, 21.1, 27.3, 27.6, 40.4, 44.5, 82.1, 98.8, 167.4, 190.1; IR 2955, 1625, 1554, 1371 cm^{-1}; HRMS: Calcd for $C_{14}H_{25}NO_2$: 239.1885. Found: 239.1883.

6,6-Diethyl-3,5-dimethyl-2-dimethylamino-5,6-dihydro-4*H*-pyran-4-one (**15c**) was prepared according to the procedure described for **15b** starting with 3-pentanone (0.505 mL, 5.0 mmole) and 3-pentanone (0.606 mL, 6.0 mmole). Chromatography of the crude material over 50 g silica gel (230-400 mesh), eluting with 3% MeOH/CH_2Cl_2 gave 665 mg (59%) of **15c**; ^{1}H NMR ($CDCl_3$): δ 0.82 (t, *J* = 7.6 Hz, 3), 0.84 (t, *J* = 7.6 Hz, 3), 1.04 (d, *J* = 7.3 Hz, 3), 1.34-1.69 (m, 4), 1.74 (s, 3), 2.37 (m, 1), 2.91 (s, 6); ^{13}C NMR ($CDCl_3$): δ 7.6, 7.8, 24.1, 25.3, 39.5, 44.2, 84.8, 87.3, 147.2, 166.0, 194.0; R_f 0.13, 5% MeOH/CH_2Cl_2; IR: 2973, 1720, 1636, 1568 cm^{-1}. HRMS: Calcd for $C_{13}H_{23}NO_2$: 225.1729. Found: 225.1734.

6,6-Diethyl-5,6-dihydro-2-dimethylamino-3-methyl-4*H*-pyran-4-one (15d(i)). 6,6-Diethyl-5,6-dihydro-2-dimethylamino-5-methyl-4*H*-pyran-4-one (15d(ii)) were prepared according to the procedure described for **15a** starting with 109.7 mg (1.52 mmol) of 2-butanone and 0.19 mL (1.88 mmol) of 3-pentanone. Yield, 99.8 mg (31%) of **15d(i)** and 53.5 mg (17%) of **15d(ii)**. **15d(i)**: ^{1}H NMR ($CDCl_3$) δ 2.93 (s, 6), 2.43 (s, 2), 1.79 (s, 3), 1.83-1.58 (m, 4), 0.88 (t, *J* = 7.5 Hz, 6); ^{13}C NMR ($CDCl_3$) δ 189.7, 166.7, 88.4, 82.8, 43.0, 39.5, 27.5, 10.7, 7.8. **15d(ii):** ^{1}H NMR ($CDCl_3$) δ 4.62 (s, 1), 2.92 (s, 6), 2.41 (q, *J* = 7.2 Hz, 1), 2.01-1.68, 1.61-1.49 (m, 4), 1.09 (d, *J* = 7.2 Hz, 3), 0.90 (t, *J* = 7.5 Hz, 3), 0.87 (t, *J* = 7.5 Hz, 3); ^{13}C NMR ($CDCl_3$) δ 193.3, 165.6, 88.1, 79.3, 44.1, 36.9, 25.6, 24.4, 11.6, 7.5, 7.4.

3-Dimethoxymethyl-6-ethyl-6-hydroxy-2-methyl-4-octanone (**19a**). Method A: A solution of 6-ethyl-6-hydroxy-2-methyl-4-octanone (1.86 mL, 10 mole) in 10 mL of dry CH_2Cl_2 at -78°C was treated with $TiCl_4$ in CH_2Cl_2 (10 mL, 10 mmole). After stirring for 30 min at 0°C, the yellow slurry was recooled to -78°C and treated with *i*-Pr_2NEt (3.7 mL, 21 mmole). After stirring for 30 min at 0°C, the red enolate was recooled to -78°C and treated with trimethyl orthoformate (2.2 mL, 20 mmole) followed by $TiCl_4$ (20 mL, 20 mmole). The reaction was stirred for 1.5 h at 0°C, quenched with 50 mL of 50% saturated NH_4Cl and stirred vigorously for

5 min. The aqueous layer was extracted with 2 x 20 mL of CH_2Cl_2. The combined organics were washed with 50 mL of 50% saturated $NaHCO_3$ and the aqueous wash was reextracted with 20 mL of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The residue was chromatographed over 50 g of silica gel (230-400 mesh), eluting with 17% ethyl acetate/hexanes to afford 2.1 g (83%) of **19a** as a pale yellow oil. Method B: A solution of 4-methyl-2-pentanone (0.625 mL, 5 mmole) 10 mL of dry CH_2Cl_2 at -78°C was treated with $TiCl_4$ in CH_2Cl_2 (5.25 mL, 5.25 mmole) and was stirred for 15 min. The yellow solution was treated with *i*-Pr_2NEt (0.915 mL, 5.25 mmole), and the resulting deep red solution was stirred for 30 min at -78°C. The red enolate was treated with 3-pentanone (0.530 mL, 5.25 mmole), warmed to 0°C, and was stirred for 1.5 h. The amber solution was cooled to -78°C, treated with *i*-Pr_2NEt (0.915 mL, 5.25 mmole), and the solution was warmed to 0°C. After 30 min, the mixture was recooled to -78°C, treated successively with trimethyl orthoformate (1.10 mL, 10 mmole) and $TiCl_4$ in CH_2Cl_2 (10 mL, 10 mmole), and stirred at 0°C for 1.5 h. The reaction was quenched with 50 mL of 50% saturated NH_4Cl, and stirred vigorously for 10 min. The aqueous layer was extracted with 2 x 20 mL of CH_2Cl_2, and the combined organics were washed with 50 mL of 50% saturated $NaHCO_3$, and dried over anhydrous K_2CO_3. The dried organics were concentrated *in vacuo* to a yellow oil and the crude material was chromatographed over 50 g of silica gel (230-400 mesh), eluting with 17% ethyl acetate/hexanes to afford 725 mg (56%) of **19a**; ^1H NMR ($CDCl_3$): δ 0.83 (t, *J* = 7.5 Hz, 3), 0.84 (t, *J* = 7.5 Hz, 3), 0.90 (d, *J* = 5.8 Hz, 3), 0.93 (d, *J* = 5.8 Hz, 3), 1.62 (m, 4), 1.99 (m, 1), 2.50 (d, *J* = 17 Hz, 1), 2.77 (d, *J* = 17 Hz, 1), 2.79 (dd, *J* = 6, 8 Hz, 1), 3.31 (s, 3), 3.34 (s, 3), 3.60 (bs, 1), 4.54 (d, *J* = 8 Hz, 1); ^{13}C NMR ($CDCl_3$): δ 7.8, 7.9, 19.0, 21.0, 27.8, 30.5, 30.7, 52.4, 52.8, 56.2, 60.5, 74.3, 105.0, 214.0; R_f 0.38, 25% ethyl acetate/hexane; IR: 3501, 2940, 1698, 1464 cm^{-1}. Anal. Calcd for $C_{14}H_{28}NO_4$: C, 64.58; H, 10.84. Found: C, 64.68; H, 10.55.

2-Dimethoxymethyl-4,5-dimethyl-5-hydroxy-3-heptanone (**19b**) was prepared according to the procedures described for **19a**. Yield of **19b** using method A was 514 mg (42%) starting with 4,6-dimethyl-5-hydroxy-3-heptanone (0.833 mL, 5 mole). Yield of **19b** using method B was 634 mg (55%) starting with 3-pentanone (0.505 mL, 5 mmole) and isobutyraldehyde (0.477 mL, 6.0 mmole). **19b**: ^1H NMR ($CDCl_3$): δ 0.84 (d, *J* = 6.7 Hz, 3), 1.05 (m, 9), 1.66 (m, 1), 2.80 (dq, *J* = 2.4, 7.1 Hz, 1), 3.10 (m, 1), 3.33 (s, 3), 3.35 (s, 3), 3.59 (dd, *J* = 2.4, 9 Hz, 1), 4.37 (d, *J* = 8.2 Hz, 1); ^{13}C NMR ($CDCl_3$): δ 7.9, 13.2, 18.9, 19.5, 30.2, 47.2, 49.0, 52.6, 56.2, 75.7, 106.8; R_f 0.29, 25% ethyl acetate/hexanes; IR: 3509, 2963, 1707, 1459 cm^{-1}. Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.42; H, 10.08.

3-(Dimethoxymethyl)-6-ethyl-6-hydroxy-2-phenyl-4-octanone (**19c**) was prepared according to the procedure described for **19a** (method B) starting with 4-phenyl-2-pentanone (810 mg, 5.00 mmol) and 3-pentanone (0.530 mL, 5.25 mmol). Yield of **19c**, 1.01 g, 63 %; ^1H NMR ($CDCl_3$) δ 7.31 (m, 2), 7.18 (m, 3), 4.31 (d, *J* = 6.7 Hz, 1), 3.66 (br, 1), 3.30 (s, 3), 3.25 (s, 3), 3.18 (dd, *J* = 6.9, 14.2 Hz, 2), 2.46 (d, *J* = 17.6 Hz,

1), 2.16 (d, *J* = 17.5 Hz, 1), 1.50-1.31 (m, 4), 1.28 (d, *J* = 6.1 Hz, 3), 0.65 (m, 6); IR: (liq.) 2967, 2939, 2882, 1698, 1460 cm^{-1}.

3-(Dimethoxymethyl)-8-(4-fluorophenyl)-6-[2-(4-fluorophenyl)ethyl]-2-phenyl-4-octanone (19d) was prepared according to the procedure described for **19a** starting with 4-phenyl-2-pentanone (3.0 g, 18.5 mmol) and 1,5-bis-(4-fluorophenyl)-3-pentanone (5.0 g, 18.2 mmol). Yield of **19d**, 6.0 g, 76%; ^1H NMR ($CDCl_3$) δ 7.30 (m, 2), 7.21 (m, 3), 7.09 (m, 4), 6.93 (m, 4), 4.30 (d, *J* = 6.4 Hz, 1), 3.98 (br s, 1), 3.27 (s, 3), 3.26 (s, 3), 3.18 (dd, *J* = 7.0, 16.3 Hz, 1), 2.58 (d, *J* = 17.4 Hz, 1), 2.54 (m, 4), 2.30 (d, *J* = 17.5 Hz, 1), 1.74 (m, 4), 1.29 (d, *J* = 6.9 Hz, 3); IR (liq.) 2937, 1698, 1601, 1510, 1495 cm^{-1}.

6,6-Diethyl-5,6-dihydro-3-(1-methylethyl)-4*H*-pyran-4-one (20a). Method A: A solution of **19a** (1.3 g, 5 mmole) in 13 mL of formic acid was diluted with 3 mL of H_2O and warmed at 40°C for 1 h. After cooling to rt, the mixture was concentrated *in vacuo* with 2 x 25 mL of toluene. The residue was chromatographed over 50 g of silica gel (230-400 mesh), eluting with 10% ethyl acetate/hexanes to provide 926 mg (95%) of **20a**; Method B: A solution of 6-ethyl-6-hydroxy-2-methyl-4-octanone (1.03 mL, 5.0 mole) in 10 mL of dry CH_2Cl_2 at -78°C was treated with $TiCl_4$ (0.577 mL, 5.25 mmole) and was stirred for 30 min at 0°C. The yellow slurry was recooled to -78°C, treated with *i*-Pr_2NEt (1.8 mL, 10.2 mmole), and stirred for 30 min at 0°C. The red enolate was recooled to -78°C and treated with trimethyl orthoformate (1.1 mL, 10 mmole) followed by $TiCl_4$ (1.1 mL, 10 mmole). The reaction was stirred for 2 h at 0°C, quenched with 50 mL of 50% saturated NH_4Cl, and was stirred vigorously for 5 min. The aqueous layer was extracted with 2 x 20 mL of CH_2Cl_2. The combined organics were washed with 50 mL of 50% $NaHCO_3$ and the aqueous wash was extracted with 20 mL of CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a pale oil (1.02 g). The residue was dissolved in 8 mL of formic acid, diluted with 2 mL of H_2O and warmed to 40°C for 1 h. The reaction was cooled and concentrated *in vacuo* with 2 x 25 mL of toluene. The residue was chromatographed over 50 g of silica gel (230-400 mesh), eluting with 10% ethyl acetate/hexanes, to afford 781 mg (80%) of **20a** as a pale yellow oil; ^1H NMR ($CDCl_3$): δ 0.89 (t, *J* = 7.5 Hz, 6), 1.03 (d, *J* = 6.9 Hz, 6), 1.62-1.83 (m, 4), 2.59 (s, 2), 2.73 (m, 1), 7.0 (s, 1); ^{13}C NMR ($CDCl_3$): δ 7.7, 21.9, 24.5, 27.8, 43.8, 84.8, 122.0, 156.6, 192.2; IR: 2970, 1671, 1615, 1463 cm^{-1}. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.49; H, 10.41.

5R*,6S*-3,5-Dimethyl-5,6-dihydro-6-(1-methylethyl)-4*H*-pyran-4-one (20b) was prepared according to the procedure described for **20a** (method A) starting from **19b** (950 mg, 4.1 mmole). Yield of **20b**, 528 mg (77%), crystallized on standing; Mp: 48-50°C; ^1H NMR ($CDCl_3$): δ 0.85 (d, *J* = 6.8 Hz, 3), 1.01 (d, *J* = 7.4 Hz, 3), 1.05 (d, *J* = 6.5 Hz, 3), 1.64 (s, 3), 1.99 (m, 1), 2.40 (dq, *J* = 2.8, 7.3 Hz, 1), 3.75 (dd, *J* = 2.8, 10 Hz, 1), 7.23 (s, 1); ^{13}C NMR ($CDCl_3$): δ 10.5, 11.3, 17.7, 19.4, 28.4, 41.6, 87.2, 111.8, 159.6, 198.4; R_f 0.46, 25% ethyl acetate/hexane; IR: 3471, 2969, 1722, 1667, 1622 cm^{-1}.

6,6-Diethyl-5,6-dihydro-3-(1-phenylethyl)-4*H*-pyran-4-one (20c) was prepared according to the procedure described for **20a** (method A) starting with **19c** (322 mg). Yield of **20c**, 0.25 g, 97%; ^{1}H NMR ($CDCl_3$) δ 7.31-7.15 (m, 5), 6.98 (s, 1), 4.00 (q, *J* = 7.2 Hz, 1), 2.53 (s, 2), 1.80-1.58 (m, 4), 1.30 (d, *J* = 7.3 Hz, 3), 0.91 (t, *J* = 7.4 Hz, 3), 0.86 (t, *J* = 7.5 Hz, 3); Anal. Calcd for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58. Found: C, 78.96; H, 8.68.

6,6-Bis[2-(4-fluorophenyl)ethyl]-5,6-dihydro-3-(1-phenylethyl)-4*H*-pyran-4-one (20d) was prepared according to the procedure described for **20a** (method A) starting with **19d**. Yield of **20d**, 1.00 g, 98 %; ^{1}H NMR ($CDCl_3$) δ 7.24 (m, 4), 7.13 (m, 2), 7.01 (m, 3), 6.98 (m, 4), 4.03 (q, *J* = 7.2 Hz, 1), 2.63 (s, 1), 2.61 (m, 4), 2.59 (s, 1), 2.03 (m, 3), 1.89 (m, 1), 1.40 (d, *J* = 7.3 Hz, 3); IR: 1669, 1612, 1510 cm^{-1}. Anal. Calcd for $C_{29}H_{28}F_2O_2$: C, 78.00; H, 6.32. Found: C, 77.73: H, 6.64.

Notes and References

1. Oppolzer, W.; Rodriguez, I. *Helv.Chim. Acta* **1993**, *76*, 1275 and references cited therein.
2. (a) Danishefsky, S.; Kato, N.; Askin, D.; Kerwin Jr., J. F. *J. Am. Chem. Soc.* **1982**, *104*, 360. (b) Danishefsky, S.; Larson, E.; Askin, D.; Kato, N. *J. Am. Chem. Soc.* **1985**, *107*, 1246. (c) Danishefsky, S.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2455. (d) Danishefsky, S.; Pearson, W. H.; Harvey, D. F.; Maring, C. J.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1256. (e) Danishefsky, S.; Maring, C. J *J. Am. Chem. Soc.* **1985**, *107*, 1269. (f) Danishefsky, S.; Larson, E.; Askin D. *J. Am. Chem. Soc.* **1982**, *104*, 6457. (g) Danishefsky, S.; Harvey, D. F.; Quallich, G.; Uang, B. J. *J. Org. Chem.* **1984**, *49*, 392. (h) Danishefsky, S.; Harvey, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 6647.
3. Danishefsky, S.; Kerwin Jr., J. F.; Kobayashi, S. *J. Am. Chem. Soc.* **1982**, *104*, 358.
4. (a) Gao, Q.; Maruyama, T.; Mouri, M.; Yamamoto, H. *J. Org. Chem.* **1992**, 1951. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (c) Danishefsky, S.; Pearson, W. H.; Harvey, D. F. *J. Am. Chem. Soc.* **1984**, *106*, 2456.
5. Peterson, J. R.; Kirchhoff, E. W. *Synlett* **1990**, 394.
6. Oppolzer, W.; Rodriguez, I. *Helv.Chim. Acta* **1993**, *76*, 1282.
7. Luke, G. P.; Morris, J. *J. Org. Chem.* **1995**, *60*, 3013.
8. (a) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215. (b) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047.
9. Morris, J.; Luke, G. P.; Wishka, D. G. *J. Org. Chem.* **1996**, *61*, 3218.
10. The regioselective generation of the exo enolate was suggested by a previous experiment in which a quantitative recovery of 6-deutero-3-hydroxy-2-methyl-5-heptanone was obtained when the titanium enolate derived from **7** was quenched with 5% DCl/D_2O; see reference 7.

(*Received* 13 *September* 1996; *revised* 7 *October* 1996; *accepted* 8 *October* 1996)