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A Three-Step Route to a Tricyclic Steroid Precursor

Douglass F. Taber* and Ritesh B. Sheth

Department of Chemistry & Biochemistry, University of Delaware, Newark, Delaware 19716

taberdf@udel.edu

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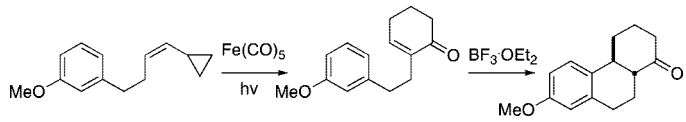
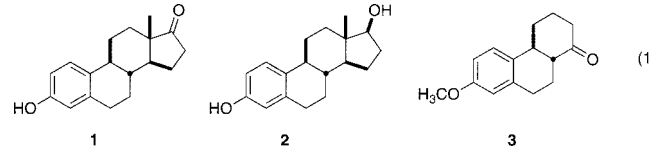


2-Alkyl cyclohexenones are useful intermediates for organic synthesis. The Wittig reaction of a series of aldehydes with (cyclopropylmethyl)triphenylphosphonium bromide delivered the corresponding alkenyl cyclopropanes. UV irradiation in the presence of $Fe(CO)_5$ converted the alkenyl cyclopropanes to the 2-substituted cyclohexenones. This approach enabled a three-step synthesis of the tricyclic core of estrone methyl ether.

Introduction

Estrone **1** and estradiol **2** (eq 1), important hormones that control the menstruation cycle of mammals, are an attractive research area due to their high biological activity and many pharmaceutical applications. A variety of synthetic strategies have been published for the synthesis of estrone and its derivatives.[1] The first total synthesis of estrone was published in 1948 by Anner and Miescher.[1a] The tricyclic phenanthrenone core **3** played a key role in that synthesis and is a potentially useful intermediate for steroid syntheses.[2]



(1)

We envisioned (Scheme 1) that aldehyde **4a** could be homologated to the corresponding alkenyl cyclopropane by Wittig reaction with the commercially available (cyclopropylmethyl)triphenylphosphonium bromide **5**.[3] UV irradiation of the alkenyl cyclopropane **6a** so prepared in the presence of $Fe(CO)_5$ under a CO atmosphere[4] would then lead to the corresponding cyclohexenone **7a**. Acid-catalyzed cyclization would then deliver the tricyclic ketone **3**, in just three steps from the commercial aldehyde **4a**.

Results and Discussion

2-Alkyl cyclohexenones are important intermediates for target-directed synthesis.[5] While several methods have been

(1) For the Bachmann−Miescher estrone synthesis, see: (a) Anner, G.; Miescher, K. *Helv. Chim. Acta* **1948**, *31*, 2173. (b) Bachmann, W. E.; Cole, W.; Wilds, A. L. *J. Am. Chem. Soc.* **1940**, *62*, 824. (c) Bachmann, W. E.; Kushner, A. C.; Stevenson, A. C. *J. Am. Chem. Soc.* **1942**, *64*, 976. For a review of synthetic routes to estrone, see: (d) Quinkert, G.; Stark, H. *Angew. Chem., Int. Ed.* **1983**, *22*, 637. For more recent references, see: (e) Vollhardt, K. P. C. *Pure Appl. Chem.* **1985**, *57*, 1819. (f) Lecker, S. H.; Nguyen, N. H.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 856. (g) Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28. (h) Michellys, P.-Y.; Pelliser, H.; Santelli, M. *Tetrahedron Lett.* **1993**, *34*, 1931. (i) Trost, B. M.; Shil, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421. (j) Sakamoto, Y.; Yasuharu, H.; Takahashi, T. *Synlett* **1995**, 231. (k) Quinkert, G.; Del Grosso, M.; Doring, A.; Doring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmerman, G.; Durner, G. *Helv. Chim. Acta* **1995**, *78*, 1345. (l) Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 7403. (m) Ouellet, L.; Langlois, P.; Deslongchamps, P. *Synlett* **1997**, 689. (n) Tietze, L. F.; Nobel, T.; Spescha, M. *J. Am. Chem. Soc.* **1998**, *120*, 8971. (o) Hu, Q.-Y.; Rege, P. D.; Corey, E. J *J. Am. Chem. Soc.* **2004**, *126*, 5984. (p) Pattenden, G.; Gonzalez, M. A.; McCulloch, S.; Walter, A.; Woodhead, S. J. *Proc. Nat. Acad. Sci.* **2004**, *101*, 12024. (q) Soorukram, D.; Knochel, P. *Org. Lett.* **2007**, *9*, 1021.

(2) For previous preparations of the tricyclic ketones **3** and **8**, see: (a) Birch, A. J.; Smith, H.; Thornton, R. E *Chem. Ind.* **1956**, 1310. (b) Birch, A. J.; Smith, H.; Thornton, R. E. *J. Chem. Soc.* **1957**, 1339. (c) Ansell, M. F.; Ducker, J. W. *J. Chem. Soc.* **1961**, 206. (d) Wiley, R. H.; Crawford, T. H.; Bray, N. F. *J. Polym. Sci., Part B: Polym. Lett.* **1965**, *3*, 99. (e) Nagata, W.; Terasawa, T.; Tori, K. *J. Am. Chem. Soc.* **1964**, *86*, 3746. (f) Sundar, N. S.; Subba Rao, G. S. *J. Chem. Res., Synop.* **1982**, 1381. (g) Varech, D.; Lacombe, L.; Jacques, J. *New J. Chem.* **1984**, *8*, 445. (h) Thompson, H. W.; Long, D. J. *J. Org. Chem.* **1988**, *53*, 4201.

(3) For the preparation of (cyclopropylmethyl)triphenylphosphonium bromide, see: (a) Maercker, A. *Angew. Chem., Int. Ed.* **1967**, *6*, 557. (b) Schweizer, E. E.; Thompson, J. G.; Ulrich, T. A. *J. Org. Chem.* **1968**, *33*, 3082. For the utility of (cyclopropylmethyl)triphenylphosphonium bromide, see: (c) Kataoka, F.; Shimizu, N.; Nishida, S. *J. Am. Chem. Soc.* **1980**, *102*, 711. (d) Cavasotto, C. N.; Liu, G.; James, S. Y.; Hobbs, P. D.; Peterson, V. J.; Bhattacharya, A. A.; Kolluri, S. K.; Zhang, X.; Leid, M.; Abagyan, R.; Liddington, R. C.; Dawson, M. I. *J. Med. Chem.* **2004**, *47*, 4360.

(4) For the development of Fe-mediated cyclocarbonylation, see: (a) Taber, D. F.; Kanai, K.; Jiang, Q.; Bui, G. *J. Am. Chem. Soc.* **2000**, *122*, 6807. (b) Taber, D. F.; Bui, G.; Chen, B. *J. Org. Chem.* **2001**, *66*, 3423. (c) Taber, D. F.; Joshi, P. V.; Kanai, K. *J. Org. Chem.* **2004**, *69*, 2268.

(5) For examples of the utility of 2-alkyl cyclohexenones in target-directed synthesis, see: (a) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555. (b) Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928. (c) Iwamatsu, S.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625. (d) Coelho, F.; Diaz, G. *Tetrahedron* **2002**, *58*, 1647.

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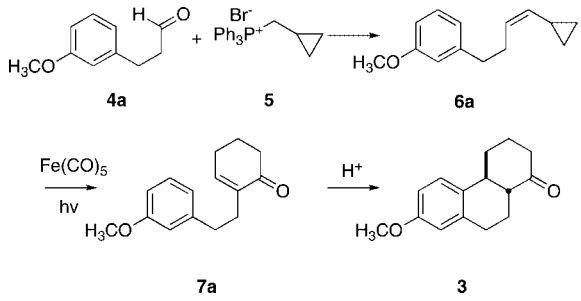
SCHEME 1



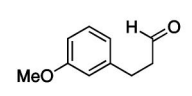
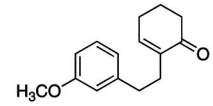
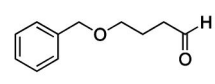
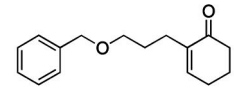
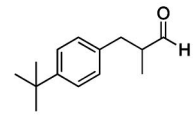
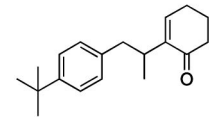
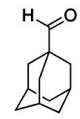
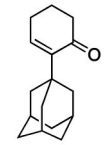
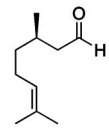
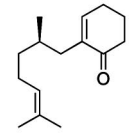
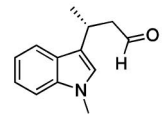
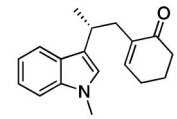
developed to prepare such cyclohexenones, these routes tend to be either low-yielding or multistepped.[6] There were two challenges to be overcome in developing the route to 2-alkylcyclohexenones outlined in Scheme 1: development of the Wittig reaction and optimization of the Fe-mediated cyclocarbonylation.

Development of the Wittig Reaction. We initially performed the Wittig reaction utilizing 1 equiv of commercial (cyclopropylmethyl)triphenylphosphonium bromide and 1 equiv of potassium *tert*-butoxide at cryogenic temperatures. This protocol led to modest yields, with some unreacted aldehyde. During optimization, we found that increasing both base and phosphonium salt to a slight excess increased conversion. While maintaining the slight excess of phosphonium bromide, we doubled the amount of base, which led to complete conversion and high yields. Finally, we found that the reaction could be carried out at room temperature. The products (Table 1) were isolated as a mixture of both the *Z* and *E* isomers of the alkenyl cyclopropane, which was of no consequence for the subsequent cyclocarbonylation.

Optimization of the Fe-Mediated Cyclocarbonylation. We initiated carbonylation studies using the conditions that we had previously developed.[6] We found that using less than 1 equiv of $Fe(CO)_5$ reduced the conversion rate, while adding greater than 2 equiv did not lead to significantly higher conversions. Increasing the concentration of the solution typically lowered conversion. We did find that the conversion and yield improved when the mixture was agitated periodically, providing for an exchange between the product and starting material forming the thin film that was being irradiated. We maintained a CO atmosphere in each of the runs, even though CO is formed during the irradiation of the $Fe(CO)_5$.

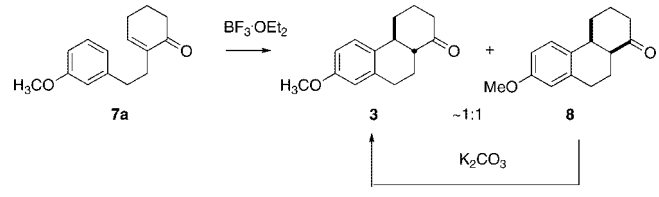
During the carbonylation of **6d**, we observed a significantly lower conversion of the alkenyl cyclopropane to the cyclohexenone **7d**. It was our hypothesis that the steric bulk of the molecule hindered the carbonylation. When we ran the photolysis without autocooling and so warmer, the conversion improved significantly. This two-step conversion appears to be a versatile and convenient way to prepare 2-alkyl cyclohexenones from the corresponding aldehydes.[7]

TABLE 1. Witting Reaction and Carbonylation

Entry	Aldehyde	Wittig Yield (%)	Cyclohexenone	Carbonylation Yield (%)
1	 4a	93	 7a	89
2	 4b	84	 7b	89
3	 4c	78	 7c	86
4	 4d	98	 7d	72[a,b]
5	 4e	89	 7e	86
6	 4f	88	 7f	85

[a] Autocooling in Rayonet was turned off. [b] For a previous preparation of **3d**, see ref 8.

SCHEME 2



Cyclization of the Enone. We envisioned (Scheme 2) that a variety of Lewis acids could effect the cyclization of the enone **3**.[5b,9] We initiated our studies with $BF_3{\cdot}OEt_2$ and $TiCl_4$. While both Lewis acids were efficient in forming the tricyclic ring, $BF_3{\cdot}OEt_2$ was milder in its reaction with the cyclohexenone, leading to less decomposition and thus higher yield. We found

(6) For previous preparations of 2-alkyl cyclohexenones, see: (a) Taber, D. F.; Gunn, B. P.; Bruce, P. *J. Org. Chem.* **1979**, *44*, 450. (b) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. (c) Armitage, M. A.; Lathbury, D. C.; Mitchell, M. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, *12*, 1551. (d) Abbas, A. A.; Kobayashi, Y. *Tetrahedron Lett.* **2003**, *44*, 119. (e) Takeishi, K.; Sugishima, K.; Sasaki, K.; Tanaka, K. *Chem. Eur. J.* **2005**, *10*, 5681.

(7) This approach is not useful for 2-aryl cyclohexenones. The iron reactions proceed with >90% yield but only to about 20% conversion. We believe that the lower conversion is a result of the competing absorption of UV radiation by the aryl enone. For practical routes to 2-aryl cyclohexenones, see: (a) Bosse, F.; Tunoori, A. R.; Niestro, A. J.; Gronwald, O.; Maier, M. E. *Tetrahedron* **1996**, *52*, 9485. (b) Prasad, A. S. B.; Knochel, P. *Tetrahedron* **1997**, *53*, 16711. (c) Kim, J.; Kulawiec, R. *Tetrahedron Lett.* **1998**, *39*, 3107. (d) Felpin, F. *J. Org. Chem.* **2005**, *70*, 8575.

(8) Reetz, M. T.; Heimbach, H. *Chem. Ber.* **1983**, *116*, 3702.

(9) For previous examples of acid-mediated cyclization of cyclohexenones onto arenes, see: (a) Pepin, J. J.; Andre-Louisfert, J.; Bisagni, E *Bull. Soc. Chim. Fr.* **1970**, *8*−*9*, 3038. (b) Hauser, F. M.; Caringal, Y. *J. Org. Chem.* **1990**, *55*, 555. (d) Bie, P. Y.; Zhang, C. L.; Peng, X. J.; Chen, B.; Yang, Y.; Pan, X. F. *Chem. J. Chin. Univ.* **2003**, *24*, 1219.

that by adding the Lewis acid slowly at 0 °C, we could also minimize decomposition.

The tricyclic ketone was approximately a 1:1 mixture of *trans* and *cis* diastereomers **3** and **8**. As had been described,[2] the *trans* diastereomer **3** could be separated by fractional crystallization. Alternatively, the two diastereomers could be efficiently separated by column chromatography. The isolated *cis* diastereomer **8** could then be epimerized to the 1:1 mixture by heating to reflux with K_2CO_3 in THF. Using this approach, one could prepare gram quantities of the crystalline *trans* ketone **3**.

Conclusion

We expect that the aldehyde to 2-alkyl cyclohexenone conversion described here will make such cyclohexenones more readily available as intermediates for target-directed synthesis. We also envision that this facile new preparation of the ketone **3** will facilitate future steroid syntheses.

Experimental Section

1-(4-Cyclopropylbut-3-enyl)-3-methoxybenzene 6a. Potassium *tert*-butoxide (1.0 M solution in THF, 50 mL, 50 mmol) was added over 20 min to a suspension of (cyclopropylmethyl)triphenylphosphonium bromide (10.0 g, 25 mmol) in 25 mL of dry THF at 0 °C. The external cooling was removed, and the mixture was stirred for 30 min. The aldehyde **4a** (3.28 g, 20 mmol) was added, and the solution was stirred at room temperature for 1 h. The mixture was quenched with 1 N HCl (50 mL) and then partitioned between water and EtOAc (3 × 100 mL). The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed to give the alkenyl cyclopropane **6a** (3.76 g, 93% yield, 77:23 *Z*/*E*) as an oil. TLC $R_f = 0.62$ (9:1 hexanes/EtOAc); ^{1}H NMR (*Z*) δ 7.19 (t, $J = 7.8$ Hz, 1H), 6.72−6.84 (m, 3H), 5.33−5.38 (m, 1H), 4.76 (t, $J = 10.8$ Hz, 1H), 3.79 (s, 3H), 2.61−2.72 (m, 2H), 2.44−2.52 (m, 2H), 1.44−1.53 (m, 1H), 0.63−0.72 (m, 2H), 0.27−0.31 (m, 2H); ^{13}C NMR (*Z*) δ CH_3: 55.1 CH_2: 36.2, 29.4, 6.8 CH: 134.5, 129.2, 127.0, 120.9, 114.2, 111.0, 9.5 C: 159.6, 143.8; ^{1}H NMR (*E*) δ 7.19 (t, $J = 7.8$ Hz, 1H) 6.72−6.84 (m, 3H), 5.52−5.57 (m, 1H), 5.01 (dd, $J = 15.2$, 8.4 Hz, 1H), 3.79 (s, 3H), 2.61−2.72 (m, 2H), 2.25−2.32 (m, 2H), 1.30−1.36 (m, 1H), 0.63−0.72 (m, 2H), 0.27−0.31 (m, 2H); ^{13}C NMR (*Z*) δ CH_3: 55.1, CH_2: 36.1, 29.4, 6.4, CH: 134.4, 129.2, 127.2, 120.9, 114.2, 111.0, 9.5 C: 159.6, 143.8; IR 2935, 1598, 1487, 1455, 1258 cm^{-1}; MS *m*/*z* (%) 202 (M, 30), 137 (65), 121 (100); HRMS calcd for $C_{14}H_{18}O$ 202.1358, obsd 202.1360.

2-(3-Methoxyphenethyl)cyclohex-2-enone 7a. To the alkenyl cyclopropane **6a** (202 mg, 1.0 mmol) in 15 mL of 2-propanol (0.075 M) was added $Fe(CO)_5$ (392 mg, 2.0 mmol). The reaction vessel was purged with CO, a CO balloon was attached, and the mixture was photolyzed for 8 h at room temperature in a Rayonet apparatus (300 nm) set for autocooling. The reaction was halted every 2 h to agitate the tube inside the larger tube, after which photolysis was restarted. At the end of the irradiation, DBU (304 mg, 2.0 mmol) was added, and the mixture was stirred at room temperature for 1 h under nitrogen. The mixture was diluted with 40 mL of EtOAc, filtered through a small pad of packed silica gel, and then subsequently concentrated. The residue was chromatographed to give 2 mg of unreacted **2a** and 202 mg of **7a** (89% yield based on **6a** not recovered) as an oil. TLC $R_f = 0.17$ (9:1 hexanes/EtOAc); ^{1}H NMR δ 7.16 (t, $J = 8.4$ Hz, 1H), 7.07 (d, $J = 9.2$ Hz, 1H), 6.81 (t, $J = 9.2$ Hz, 1H), 6.73 (m, 1H), 6.61 (m, 1H), 3.78 (s, 3H), 2.68 (m, 2H), 2.45 (m, 4H), 2.28 (m, 2H), 1.98 (m, 2H); ^{13}C NMR δ CH_3: 55.4, CH_2: 38.7, 35.1, 31.7, 26.1, 23.1, CH: 149.6, 129.2, 121.0, 114.1, 111.2, C: 199.4, 159.5, 143.7, 139.2; IR 3442, 2960, 1734, 1206, 1099 cm^{-1}; MS *m*/*z* (%) 230 (M, 8), 221 (7), 163 (15), 135 (95), 107 (100); HRMS calcd for $C_{15}H_{18}O_2$ 231.1385, obsd 231.1391.

7-Methoxy-2,3,4,4a,10,10a-hexahydrophenanthren-1(9*H*)-one 3 and 8. $BF_3 \cdot OEt_2$ (1.0 M solution in CH_2Cl_2, 2 mL, 2 mmol) was added over 5 min to cyclohexenone **7a** (230 mg, 1.0 mmol) in 5 mL of dry CH_2Cl_2 (0.20 M) at 0 °C. The solution was stirred at room temperature for 3 h, quenched with water (5 mL), and then partitioned between water and methylene chloride. The combined organic extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed using 80:20 PE/MTBE as an elution solvent to give the phenanthrenone **3** (92 mg, 40% yield) as a solid and phenanthrenone **8** (90 mg, 38% yield, 78% yield overall) as an oil. The *cis* diastereomer **8** (85 mg, 0.37 mmol) was then heated to reflux with a suspension of K_2CO_3 (690 mg, 5 mmol) in dry THF (2 mL) overnight to epimerize the phenanthrenone to a 1:1 mixture of diastereomers. For phenanthreone **3**: mp = 106−109 °C; TLC $R_f = 0.45$ (8:2 hexanes/EtOAc (double elution)); ^{1}H NMR δ 7.23 (d, $J = 9$ Hz, 1H), 6.75 (dd, $J = 9$, 3 Hz, 1H), 6.66 (d, $J = 3$ Hz, 1H), 3.78 (s, 3H), 2.84 (m, 2H), 2.73 (td, $J = 12$, 3 Hz, 1H), 2.61 (m, 1H), 2.41−2.53 (m, 2H), 2.35 (td, $J = 12$, 3 Hz, 1H), 2.18−2.30 (m, 2H), 1.86 (tdd, $J = 13$, 5, 4 Hz, 1H), 1.61−1.77 (m, 2H); ^{13}C NMR δ CH_3: 55.2, CH_2: 44.3, 30.5, 29.3, 26.3, 21.7, CH: 138.0, 113.8, 112.0, 52.7, 44.3, C: 212.0, 157.8, 138.0, 131.2, 126.9; IR 1720, 1615 cm^{-1}; MS *m*/*z* (%) 230 (M, 100), 213 (55), 187 (30), 160 (25), 135 (43); HRMS calcd for $C_{14}H_{18}O$ 230.1307, obsd. 230.1302. For phenanthrenone **8**: TLC $R_f = 0.42$ (8:2 hexanes/EtOAc (double elution)); ^{1}H NMR δ 7.05 (d, $J = 9$ Hz, 1H), 6.75 (dd, $J = 9$, 3 Hz, 1H), 6.62 (d, $J = 3$ Hz, 1H), 3.78 (s, 3H), 2.84 (m, 2H), 2.73 (td, $J = 12$, 3 Hz, 1H), 2.61 (m, 1H), 2.41−2.53 (m, 2H), 2.35 (td, $J = 12$, 3 Hz, 1H), 2.18−2.30 (m, 2H), 1.86 (tdd, $J = 13$, 5, 4 Hz, 1H), 1.61−1.77 (m, 2H); ^{13}C NMR δ CH_3: 55.6, CH_2: 38.8, 30.7, 29.0, 24.5, 22.6, CH: 129.7, 113.6, 112.7, 50.6, 40.4, C: 214.4, 157.8, 137.0, 131.2, 126.9; IR 1720, 1615 cm^{-1}; MS *m*/*z* (%) 230 (M, 100), 213 (4), 187 (40), 159 (35), 147 (31), 121 (19); HRMS calcd for $C_{14}H_{18}O$ 230.1307, obsd 230.1302.

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Supporting Information Available: General experimental procedures, experimental procedures for **2b**−**2f** and **3b**−**3f**, details of the photochemical apparatus, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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