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A Synthetic Alternative to the Type-II Intramolecular 4 + 3 Cycloaddition Reaction

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Abstract: Oxyallyl cations generated in situ from dihaloketones have been found to undergo the Favorskii rearrangement in preference to an intramolecular Type-II 4 + 3 cycloaddition reaction in trifluoroethanol and hexafluoropropan-2-ol solvents, generating acrylate esters with high cis selectivity. A synthetic alternative to the intramolecular Type-II 4 + 3 cycloaddition has been developed on the basis of intramolecular enolate alkylation to close a 7-membered ring with an exocyclic double bond.

The 4 + 3 cycloaddition reaction between a diene and an allylic cation is a powerful method for the synthesis of 7-membered rings.[1] In the intramolecular series, Harmata has delineated six possible ways of linking the diene with the allylic cation (Figure 1).[2] To date, only examples of the Type-I system have been reported in the literature.

As part of a synthetic approach to the diterpene ingenol, we have investigated the Type-II intramolecular 4 + 3 cycloaddition reaction of an oxyallyl cation tethered to the 3-position of a furan as a means to construct the [4.4.1] bicyclic skeleton (BC ring system) of the natural product (Scheme 1).[3] We envisage that stereoselective reduction of the bridgehead double bond system **1** offers a means to access the thermodynamically unfavorable trans ring junction (in−out stereochemistry)[4] deemed essential for the biological activity of ingenol.[5,6] Here, we report our attempts to achieve such a transformation, the problems associated with such an approach, and an alternative, more successful method for the construction of the desired ring system **1** based on intramolecular enolate alkylation.

In general, oxyallyl cations are too unstable to be isolated and are typically generated in situ. Although a variety of precursors can be used to generate oxyallyl cations, α-haloketones have found most application in the chemical literature.[1,2] Construction of α-dihaloketones **5** and **6** required to test the proposed Type-II cyclization are shown in Scheme 2. Homologation of 3-furfuryl alcohol **2**[7] was carried out via a known three-step sequence.[8] Conversion of alcohol **3** to the corresponding bromide followed by displacement with dimethylmalonate and Krapcho decarboxylation gave monoester **4**, which could be converted into the dichloroketone **5** or dibromoketone **6** using Barluenga's methodology.[9]

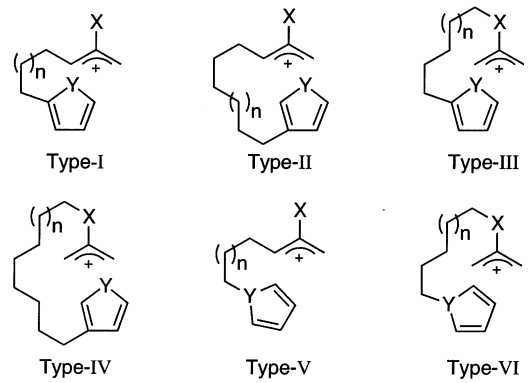
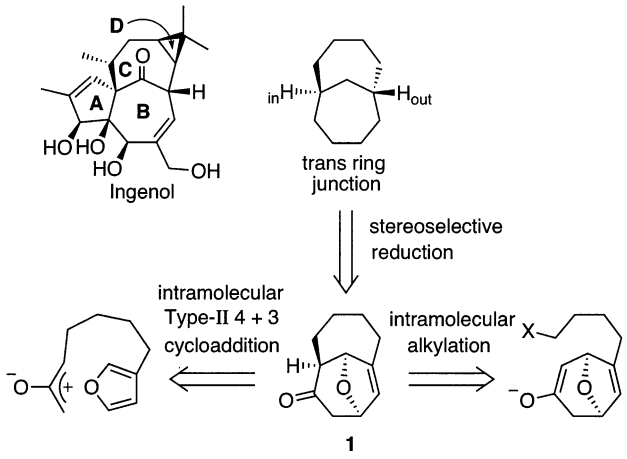


FIGURE 1. Intramolecular 4 + 3 cycloaddition reactions of allylic cations.

SCHEME 1



(1) (a) Noyori, R.; Hayakawa, Y. *Org. React. (N.Y.)* **1983**, *29*, 163−344. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611.

(2) (a) Harmata, M. *Tetrahedron* **1997**, *53*, 6235. (b) Harmata, M. In *Advances in Cycloaddition*; Lautens, M., Ed.; JAI: Greenwich, 1997; Vol. 4, pp 41−86.

(3) Harmata has shown the intramolecular Type-I cycloaddition reaction to be an excellent method for the rapid assembly of the isoingenol skeleton (cis ring junction between the B- and C-rings): Harmata, M.; Elahmad, S.; Barnes, C. L. *Tetrahedron Lett.* **1995**, *36*, 1397.

(4) Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097.

(5) Total syntheses of ingenol: (a) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726. (b) Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am.Chem. Soc.* **2003**, *125*, 1498. For a review of approaches to the synthesis of ingenol, see: Kim, S.; Winkler, J. D. *Chem. Soc. Rev.* **1997**, *26*, 387. For more recent work, see: (c) Nakamura, T.; Matsui, T.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 3032. (d) Rigby, J. H.; Hu, J.; Heeg, M. J. *Tetrahedron Lett.* **1998**, *39*, 2265. (e) Winkler, J. D.; Kim, S.; Harrison, S.; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296. (f) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D. *Tetrahedron Lett.* **2000**, *41*, 3927. (g) Tang, H.; Yusuff, N.; Wood, J. L. *Org. Lett.* **2001**, *3*, 1563. (h) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799.

(6) Isomerization of a cis- to trans-ring system via formation and stereoselective reduction of a bridgehead double bond is the key feature in Rigby's elegant approach to ingenol: Rigby, J. H.; de Sainte Claire, V.; Cuisiat, S. V.; Heeg, M. J. *J. Org. Chem.* **1996**, *61*, 7992. See also ref 5d,h.

(7) Prepared by reduction of commercially available 3-furoic acid (lithium aluminium hydride, THF, rt, 83%). Wang, E. S.; Choy, Y. M.; Wong, H. N. C. *Tetrahedron* **1996**, *52*, 12137.

(8) New, D. G.; Tesfai, Z.; Moeller, K. D. *J. Org. Chem.* **1996**, *61*, 1578.

(9) Barluenga, J.; Llavona, L.; Concellón, J. M.; Yus, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 297.

† To whom correspondence regarding the X-ray crystal structure should be addressed.

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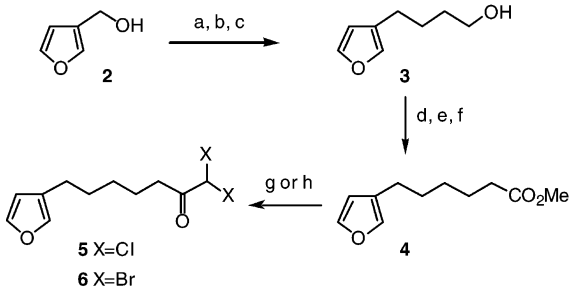
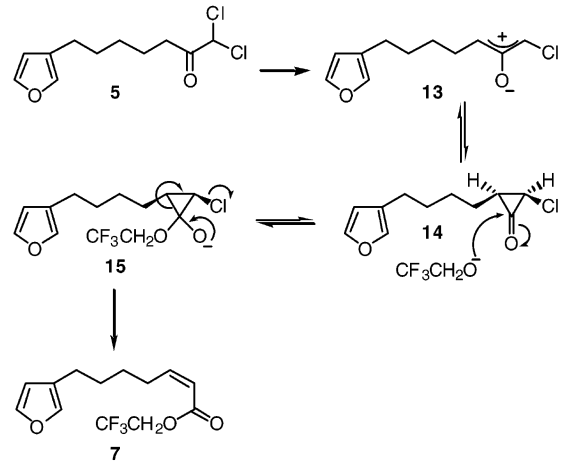
SCHEME 2[a]



[a] Reagents and conditions: (a) PBr_3, pyridine, Et_2O; (b) allylMgCl, THF; (c) Sia_2BH, then NaOH, H_2O_2, 45% over three steps; (d) CBr_4, Ph_3P, CH_2Cl_2, rt, 3 h, 89%; (e) dimethyl malonate, NaH, DMF, THF, reflux, 24 h, 70%; (f) NaCl, DMSO, H_2O, reflux, 3 h, 90%; (g) Cy_2NLi, CH_2Cl_2, THF, −78 °C, 2 h, 64% **5**; (h) LDA, CH_2Br_2, THF, −78 °C, 2 h, 63% **6**.

SCHEME 3



Intramolecular Type-II 4 + 3 cycloaddition reactions of **5** and **6** were attempted under a variety of standard conditions, including $LiClO_4/Et_3N/Et_2O$, Et_3N/trifluoroethanol (TFE), and NaTFE/TFE.[10] Reactions proceeded slowly at room temperature to give complex mixtures of products. Analysis of ^{1}H NMR of the crude reaction mixtures suggested retention of the monosubstituted furan functionality under almost all conditions.[11] In the case of reactions in trifluoroethanol, slow conversion to a mixture of trifluoroethyl acrylic esters **7** and **8** was observed, the ratio of which varied with the base used to generate the oxyallyl cation (Table 1, entries 1−3).

The formation of **7** and **8** can be ascribed to a competing Favorskii rearrangement in preference to the desired 4 + 3 cycloaddition reaction (Scheme 3). The cis double-bond geometry in **7** was assigned on the basis of coupling constants in the ^{1}H NMR spectrum and is consistent with a stereospecific disrotative ring closure of an oxyallyl cation **13** to a *cis*-cyclopropane **14**, followed by a stereospecific S_N2-type ring opening via **15** to **7**.[12] The formation of the 2-methylene ester **8** can be ascribed to elimination of an α-chloromethyl ester formed via opening of the alternative C−C bond in the cyclopropane intermediate **15** or via Favorskii rearrangement of a 1,3-dichloroketone formed via 1,3-Cl migration in **5**.

Products derived from Favorskii rearrangements have been observed as minor components in 4 + 3 cycloaddition reactions of oxyallyl cations,[13] but their formation is generally minimized by the use of the nonnucleophilic solvent, trifluoroethanol. Recourse to the even less nucleophilic solvent hexafluoropropan-2-ol suppressed the Favorskii rearrangement of dichloroketone **5** and promoted formation of the desired cycloadduct **9** (albeit in low yield), thus establishing for the first time that the Type-II 4 + 3 cyclization mode is possible (Table 1, entries 4 and 5). Unfortunately, application of these conditions to the dibromoketone **6** only gave trace amounts of the desired cycloadduct **11**, with *cis*-alkene **10** now predominating (Table 1, entry 6).

The results in Table 1 clearly demonstrate that although the Type-II cyclization mode is possible, it is never going to be synthetically viable under these reaction conditions. Although a range of alternative substrates for oxyallyl cation formation can be envisaged which might avoid the problem of competing Favorskii rearrangement,[14] we chose instead to investigate a complementary approach to the requisite ring system **1**, involving a novel intramolecular enolate alkylation to close a 7-membered ring (Scheme 1).[15] Analysis of simple molecular models suggested the conformation required for an intramolecular S_N2 reaction to occur is only accessible on the face of the enolate opposite the oxygen bridge. Furthermore, cyclization of the desired enolate appeared to be clearly favored over its regioisomer, thereby allowing us to potentially exploit thermodynamic conditions for enolate generation. This strategy was brought into practice as follows (Scheme 4). Intermolecular 4 + 3 cycloaddition of 3-substituted furan **3** with the oxyallyl cation generated in situ from 1,1,3-trichloropropan-2-one proceeded readily to provide alcohol **16** after dehalogenation. A variety of bases (KH, NaH, LDA, KHMDS, Cs_2CO_3, KO-*t*-Bu) and conditions (solvent/temperature) have been screened for the 7-membered ring closure on both tosylate **17** and bromide **18**. Potassium *tert*-butoxide proved greatly superior to other bases—in refluxing THF under high dilution conditions tosylate **17** can be closed to ketone **1** in a synthetically useful 80% yield. Notably, this reaction proceeds without cleavage of the strained ether bridge in **1**.[16] The structure of **1** has been unambiguously proven by X-ray crystallography.[17]

In conclusion, an investigation into a Type-II intramolecular 4 + 3 cycloaddition has shown the Favorskii

(10) Sendelbach, S.; Schwetzler-Raschke, R.; Radl, A.; Kaiser, R.; Henle, G. H.; Korfant, H.; Reiner, S.; Föhlisch, B. *J. Org. Chem.* **1999**, *64*, 3398.

(11) Disubstituted furans can potentially arise via an intramolecular aromatic substitution reaction. For a recent example, see: Kreiselmeier, G.; Föhlisch, B. *Tetrahedron Lett.* **2000**, *41*, 1375.

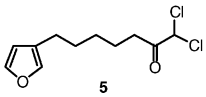
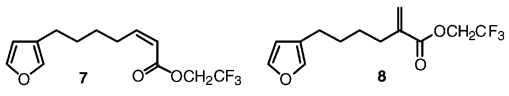
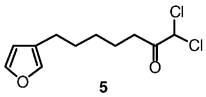
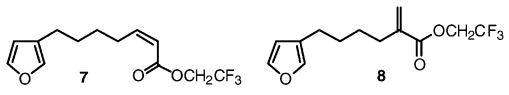
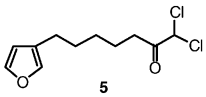
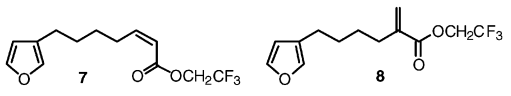
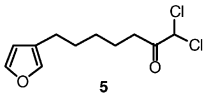
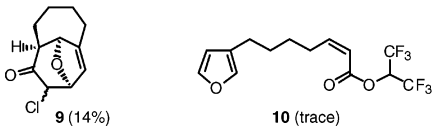
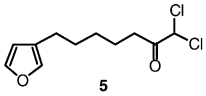
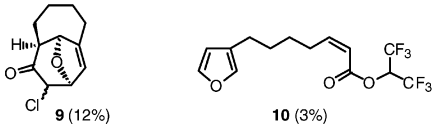
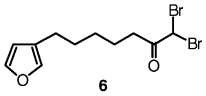
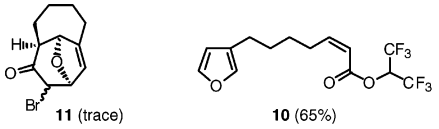
(12) Schamp, N.; De Kimpe, N.; Coppens, W. *Tetrahedron* **1975**, *31*, 2081.

(13) (a) Föhlisch, B.; Gehrlach, E.; Henle, G.; Boberlin, U.; Gekeler, M.; Geywitz, B.; Ruck, M.; Vogl, H. *J. Chem. Res., Miniprint* **1991**, 1401. (b) Reference 11. (c) Föhlisch, B.; Kreiselmeier, G. *Tetrahedron* **2001**, *57*, 10077.

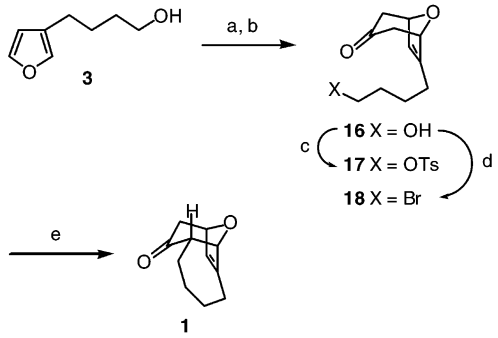
(14) For recent examples, see: (a) Myers, A. G.; Barbay, J. K. *Org. Lett.* **2001**, *3*, 425. (b) Cho, S. Y.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2891. (c) Aungst, R. A., Jr.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3553. (d) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (e) Harmata, M. *Acc. Chem. Res.* **2001**, *34*, 595 and references therein. (f) Handy, S. T.; Okello, M. *Synlett* **2002**, 489. (g) Harmata, M.; Ghosh, S. K.; Hong, X.; Wacharasindhu, S.; Kirchhoefer, P. *J. Am. Chem. Soc.* **2003**, *125*, 2058.

(15) For representative examples of 7-membered ring-closure via enolate alkylation, see: (a) Conia, J.-M.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1963**, 1930. (b) Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051. (c) Spreitzer, H.; Pichler, A.; Holzer, W.; Schlager, C. *Helv. Chim. Acta* **1998**, *81*, 40.

TABLE 1. Attempted Type-II Intramolecular 4 + 3 Cycloaddition Reactions of Dihaloketones 5 and 6

entry	dihaloketone	conditions	products (isolated yield)
1	 **5**	Et_3N (2.2 eq.), CF_3CH_2OH (0.17M), rt, 7 days	 **7** **8** 4 : 1 (62%)
2	 **5**	Et_3N (2.2 eq.), CF_3CH_2OH (0.8M), 50°C, 24h	 **7** **8** 4 : 1 (57%)
3	 **5**	$NaOCH_2CF_3$, CF_3CH_2OH, (0.8M), rt, 5days	 **7** **8** 1 : 1 (65%)
4	 **5**	Et_3N (2.2 eq.), $(CF_3)_2CHOH$ (0.8M), rt, 7 days	 **9** (14%) **10** (trace)
5	 **5**	$NaOCH(CF_3)_2$, $(CF_3)_2CHOH$ (0.8M), rt, 5 days	 **9** (12%) **10** (3%)
6	 **6**	Et_3N (2.2 eq.), $(CF_3)_2CHOH$ (0.8M), rt, 7 days	 **11** (trace) **10** (65%)

SCHEME 4[a]



[a] Reagents and conditions: (a) 1,1,3-trichloropropan-2-one, $NaOCH_2CF_3$, CF_3CH_2OH, rt, 3 days; (b) Zn, CuBr, MeOH, 2 days, 54% over two steps; (c) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 4.5 h, 64%; (d) CBr_4, Ph_3P, CH_2Cl_2, 71%; (e) *t*-BuOK, THF, reflux, 80% from **17**, 60% from **18**.

rearrangement to be the major reaction pathway for oxyallyl cations generated from dihaloketones under classical conditions.[18] The low yields of the Type-II cycloadduct have necessitated the development of an alternative approach to the same ring system based on intramolecular enolate alkylation under thermodynamic conditions. Further studies on the selective functionalization and ring opening of oxatricyclic systems such as **1** are in progress and will be reported in due course.

Experimental Section

Intermolecular 4 + 3 Cycloaddition of Furan (3). A solution of $NaOCH_2CF_3$ (10.7 mL, 21.4 mmol) in CF_3CH_2OH (10.7 mL) and 1,3,3-trichloroacetone (2.3 mL, 2.4 mmol) were added separately via syringe to alcohol **3** (1.5 g, 10.7 mmol) over 1 h at 0 °C. The reaction was allowed to warm to room temperature and stirred for 3 days. The reaction was quenched with water and extracted with diethyl ether. The organic layer was dried ($MgSO_4$) and concentrated to give a crude product that was taken up in methanol (10 mL) and added to a solution of Zn (14.8 g, 227.3 mmol) and Cu(I)Br (8.7 g, 60.6 mmol) in methanol (130 mL). The mixture was stirred at room temperature for 2 days before filtering through 10 g of Celite and the filtrate concentrated to give a residue the was dissolved in a 5% solution of HCl. The aqueous layer was extracted with diethyl

(16) Reviews on ring opening: (a) Woo, S.; Keay, B. A. *Synthesis* **1996**, 669. (b) Chiu, P.; Lautens, M. In *Topics in Current Chemistry, Vol. 190*; Metz, P., Ed.; Springer-Verlag: New York, 1997; pp 1−85. (c) Lautens, M.; Fagnou, K.; Hiebert, S. *Acc. Chem. Res.* **2003**, *36*, 48.

(17) The author has deposited X-ray coordinates with the Cambridge Crystallographic Data Center (CCDC 202411).

(18) Although determination of the optimal chain length between diene and oxyallyl cation was not the aim of this study, it may well be that other systems undergo the Type-II 4 + 3 cycloaddition with greater ease than **5** or **6**. In this respect, it is perhaps notable that to the best of our knowledge Type-I intramolecular 4 + 3 cycloadditions are only known with three or four atoms in the tether to form five- or six-membered rings, respectively.

ether and once with ethyl acetate. The combined organic layer was dried ($MgSO_4$) and concentrated a crude residue that was purified by column chromatography (3:1 60−80 petroleum ether/ethyl acetate) to give **16** (807 mg, 54% over two steps) as a light yellow oil: R_f 0.23 (3:1 ethyl acetate/60−80 petroleum ether); ν_{max} (neat) 3430 br, 2940, 1708 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.52 (m, 4 H), 1.82 (br, 1 H), 2.08 (br, 2 H), 2.27 (m, 2 H), 2.62 (m, 2 H), 3.57 (t, J = 5.3 Hz, 2 H), 4.72 (d, J = 4.9 Hz, 1 H), 4.92 (d, J = 4.5 Hz, 1 H), 5.76 (d, J = 1.6 Hz, 1 H); δ_C (90 MHz, $CDCl_3$) 23.9 (CH_2), 27.3 (CH_2), 32.6 (CH_2), 46.5 (CH_2), 46.6 (CH_2), 62.9 (CH_2), 78.0 (CH), 80.0 (CH), 126.1 (CH), 148.0 (C), 206.4 (C); m/z (EI) 196 (M^+; 97.3), 178 (43), 153 (92), 95 (100); HRMS calcd for $C_{11}H_{16}O_3Na$ ($M + Na^+$) 219.0992, found 219.0989.

Bromide (18). To a solution of alcohol **16** (1.0 g, 5.1 mmol) and carbon tetrabromide (2.1 g, 6.3 mmol) in CH_2Cl_2 (30 mL) was added portionwise triphenylphosphine (2.1 g, 8.0 mmol) at 0 °C. The mixture was stirred for 2 h while warming to room temperature. The reaction was quenched with water, followed by extraction with CH_2Cl_2. The combined organic extracts were washed with brine and dried over $MgSO_4$. Concentration of the organic layer in vacuo gave a residue that was purified by column chromatography (2:1 petroleum ether/ethyl acetate) to afford the title compound (940 mg, 71%) as a colorless oil: R_f 0.45 (3:2 petroleum ether/ethyl acetate); ν_{max} (neat) 2939, 1711 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.66 (m, 2 H), 1.89 (m, 2 H), 2.15 (m, 2 H), 2.35 (m, 2 H), 2.75 (m, 2 H), 3.42 (t, J = 6.6 Hz, 2 H), 4.79 (d, J = 4.9 Hz, 1 H), 5.00 (d, J = 4.5 Hz, 1 H), 5.85 (d, J = 3.5 Hz, 1 H); δ_C (90 MHz, $CDCl_3$) 26.09 (CH_2), 26.6 (CH_2), 32.5 (CH_2), 33.8 (CH_2), 46.5 (CH_2), 78.0 (CH), 79.4 (CH), 126.3 (CH), 148.0 (C), 206.1 (C); m/z (EI) 258 (M^+; 36.7), 217 (100), 279 (35), 137 (59); HRMS calcd for $C_{11}H_{15}O_2BrNa$ ($M + Na^+$) 281.0148, found 281.0111.

Tosylate (17). To a suspension of alcohol **16** (200.0 mg, 1.02 mmol), 4-DMAP (11.0 mg, 0.09 mmol), and triethylamine (0.63 mL, 4.52 mmol) in CH_2Cl_2 (11 mL) was added *p*-toluenesulfonyl chloride (328 mg, 1.72 mmol) in one portion with cooling in an ice−water bath. The reaction was stirred for 4.5 h while warming to room temperature and then diluted with diethyl ether (15 mL). The organic phase was washed with aqueous sodium bicarbonate solution and dried ($MgSO_4$). The crude reaction was purified by column chromatography (2:1 petroleum ether 60−80/ethyl acetate) to give **17** (227 mg, 64%): mp 42−43 °C; R_f 0.48 (2:1 60−80 petroleum ether/ethyl acetate); ν_{max} (neat) 2930, 2360, 1700, 1050 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.51 (m, 4 H), 1.99 (m, 2 H), 2.23 (m, 2 H), 2.39 (s, 3 H), 2.66 (m, 2 H), 3.96 (t, J = 6.1 Hz, 2 H), 4.67 (d, J = 4.9 Hz, 1 H), 4.90 (d, J = 4.5 Hz, 1 H), 5.71 (d, J = 1.8 Hz, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.30 (d, J = 8.3 Hz, 2 H); δ_C (90 MHz, $CDCl_3$) 22.1 (CH_3), 23.6 (CH_2), 26.8 (CH_2), 28.8 (CH_2), 46.5 (CH_2), 70.4 (CH_2), 78.0 (CH), 79.4 (CH), 126.3 (C), 128.3 (CH), 130.3 (CH), 133.4 (C), 145 (C), 147.8 (C), 206.0 (C); m/z (EI) 350 (M^+; 100), 178 (22), 135 (67), 121 (18); HRMS calcd for $C_{14}H_{14}O_3F_6S$ 350.1188, found 350.1172.

Oxatricyclic Ketone (1). To a stirred solution of KO-*t*-Bu (50 mg, 0.45 mmol) in THF (38 mL) was added a solution of **17** (120 mg, 0.34 mmol) in THF (110 mL). The mixture was refluxed for 1 h, and then a further 1.3 equiv of KO^{t}Bu (50 mg, 0.45 mmol) was added in one portion. The resulting mixture was refluxed for 30 min, by which time the reaction was seen to have gone to completion (by TLC). The reaction was quenched with saturated aqueous NH_4Cl, followed by extraction of the aqueous layer with diethyl ether. The ethereal layer was dried ($MgSO_4$) and concentrated in vacuo to afford compound **1** (47 mg, 80%) as a yellow solid: mp 72−73 °C; R_f 0.42 (3:1 60−80 petroleum ether/ethyl acetate); ν_{max} (neat) 2932, 2858, 1704, 1046 cm^{-1}; δ_H (360 MHz; $CDCl_3$) 1.14 (m, 4 H), 1.50 (m, 2 H), 1.70 (m, 2 H), 2.15 (m, 1 H), 2.26 (m, 2 H), 2.56 (dd, J = 15.8, 4.6 Hz, 1 H), 2.74 (m, 1 H), 4.72 (d, J = 4.4 Hz, 1 H), 4.97 (t, J = 1.6 Hz, 1 H), 5.64 (s, 1 H); δ_C (90 MHz, $CDCl_3$) 23.7 (CH_2), 26.1 (CH_2), 26.6 (CH_2), 38.1 (CH_2), 46.27 (CH_2), 56.2 (CH), 78.9 (CH), 82.4 (CH), 126.9 (CH), 147.5 (CH), 207.6 (C); m/z (EI) 178 (M^+; 100), 149 (24), 121 (41), 79 (27); HRMS calcd for $C_{11}H_{14}O_2$ 179.1072, found 179.1073.

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Supporting Information Available: General experimental procedures and representative procedures for 4 + 3 cycloaddition reactions/Favorskii rearrangements. Copies of ^1H and ^{13}C NMR spectra for all compounds used in this study. X-ray data for compound **1** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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