Cyclopropanation/Reduction of a 3,4-Disubstituted 2(5*H*)-Furanone: A Model for C-8 Methylation at the Taxane BC Ring Juncture

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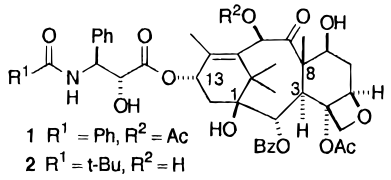
A cyclopropanation/reduction strategy is described that should prove useful for incorporation of the C-8 methyl group at the taxane BC ring juncture. Treatment of model 2(5*H*)-furanone **6** with various organocopper-based reagents resulted in γ-deprotonation to the furan oxide rather than the desired conjugate addition. This pathway was established by deuteration studies. Reaction of **6** with dimethylsulfoxonium methylide in DMSO at room temperature also led exclusively to γ-deprotonation; however, the use of excess methylide at 50 °C led to the clean formation of the desired cyclopropanated adduct **13**. While the cyclopropane ring in **13** proved resistant to various heterogeneous hydrogenation conditions, treatment with Li/liq NH_3 under careful temperature control (−78 °C to −63 °C) led to the regioselective formation of the desired ring-opened product **7** with high (16:1) diastereoselectivity.

Introduction

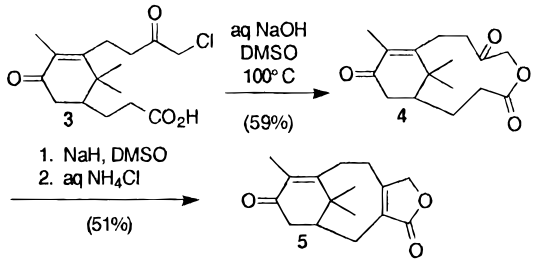
Paclitaxel (**1**)[1] is a naturally occurring taxane diterpene isolated from the stem bark of the Pacific Yew. It exhibits a wide variety of antitumor activities and is used clinically for the treatment of ovarian and breast cancers.[2] The synthesis of structural analogs of paclitaxel is an extremely important current goal. These compounds may exhibit similar or enhanced antitumor activity relative to paclitaxel (e.g. docetaxel (**2**)[3]) and can be used in studies designed to broaden the current



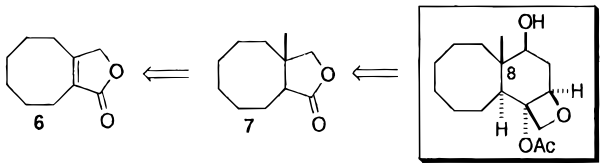
knowledge base concerning paclitaxel structure−activity relationships. In an effort toward this goal, our group has published an approach to the taxane AB ring system (Scheme 1).[4] In this work, α-chloro keto acid **3** was converted to the macrocyclic keto lactone **4**. This, in turn, yielded the taxane AB ring system **5** when subjected to thermodynamic aldol conditions.

Completion of the taxane skeleton required that we next develop a strategy suitable for elaboration of the 2(5*H*)-furanone moiety in **5** to the taxane C ring. In this paper, we report the results of our efforts aimed at developing a conjugate addition strategy for incorporating the C-8 methyl group (paclitaxel numbering) at the taxane BC ring juncture. It was recognized that conjugate addition at such a sterically crowded carbon might

Scheme 1



Scheme 2



prove challenging. Therefore, we initially focused our attention on the conjugate methylation of the model 2(5*H*)-furanone substrate **6** as a route to the corresponding adduct **7** (Scheme 2). This substrate contains the requisite 2(5*H*)-furanone functionality fused to an eight-membered carbocycle, and is readily synthesized.[5]

Results and Discussion

Conjugate addition reactions of organometallic reagents to β,β-disubstituted enoates, while uncommon, are not without precedent. Paquette and co-workers used lithium dimethylcuprate to successfully methylate bicyclic lactone **8** (eq 1).[6] Similarly, Yamamoto and Maruyama used a butylcopper/boron trifluoride complex to alkylate enoate **9** (eq 2) although the yield was modest and conversion incomplete.[7] Unfortunately, all of our attempts to convert **6** to **7** using a series of methyl cuprate and methylcopper reagents under a variety of

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(1) Also called Taxol, a registered trademark of the Bristol-Myers Squibb Company.

(2) For general reviews on a variety of subjects in this area see: (a) *Taxane Anticancer Agents*; Georg, G. I., Chen, T. T., Ojima, I., Vyasi, D. M., Eds.; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (b) *Taxol: Science and Application*; Suffness, M., Ed.; CRC: Boca Raton, 1995. (c) Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44. (d) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. *Contemp. Org. Synth.* **1994**, 47.

(3) Guenard, D.; Gueritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160−167.

(4) Chai, K. B.; Sampson, P. *J. Org. Chem.* **1993**, *58*, 6807−6813.

(5) Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972−6975.

(6) Roberts, R. A.; Schüll, V.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 2076−2084.

(7) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 3240−3241.

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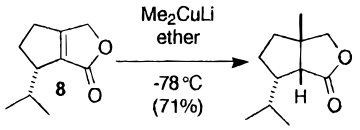
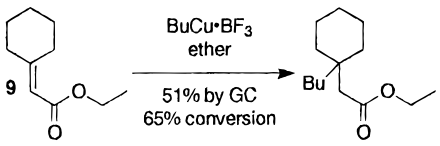


eq 1



eq 2

conditions resulted only in the efficient recovery of starting enoate **6**. The addition of Me_3SiCl[8] and the use of "higher order" cyanocuprates[9] also proved ineffective in achieving conjugate addition chemistry.

We considered two possible explanations for these results: either the β,β-disubstituted enoate **6** was too crowded to allow for reaction with the organometallic reagent, or else the desired reaction was being thwarted by a competitive γ-deprotonation pathway which would afford an aromatic furan oxide (**10**, Scheme 3). Reprotonation during workup would then regenerate starting furanone **6**. In an attempt to distinguish between these two possible scenarios, furanone **6** was treated with lithium dimethylcuprate, and the resulting reaction product was quenched with CH_3OD (Scheme 3). ^1H NMR analysis of the crude product showed 95% exchange of deuterium for *both* hydrogens of the γ-methylene group (**11**). This suggested that H/D exchange was occurring under the equilibrating conditions established in the workup. When a chloroform solution of **11** was shaken with aqueous NH_4Cl for 20 min, there was no evidence for D/H exchange based upon ^1H NMR spectral analysis. This suggested that ND_4Cl would be a more appropriate kinetic quench for the cuprate reaction. Indeed, when **6** was again treated with lithium dimethylcuprate and the reaction was quenched with solid ND_4Cl, only the monodeuterated furanone **12** was observed in the ^1H NMR spectrum of the crude reaction product. This established that the attempted conjugate addition of lithium dimethylcuprate (and, presumably, the other organocopper reagents examined) to furanone **6** were thwarted by competing γ-deprotonation.

It is noteworthy that a similar γ-deprotonation pathway was not observed by Paquette and co-workers during their successful β-methylation of 2(5*H*)-furanone **8** (eq 1).[6] Such a γ-deprotonation pathway in **8** may be disfavored by the significant increase in strain that would be expected on rehybridizing the γ-carbon from sp^3 to sp^2 in this already strained ring system. In contrast, the observed conjugate addition pathway actually results in a relief of ring strain as the β-carbon undergoes rehybridization from sp^2 to sp^3. In our system, the presence of an eight-membered carbocyclic ring rather than a five-membered ring fused to the 2(5*H*)-furanone means that the additional sp^2 hydridized carbon in the dienolate **10** can be accommodated without a significant increase in ring strain. Similarly, no significant decrease in ring strain would be expected on β-conjugate methylation. Therefore, it is reasonable to find that the propensity for γ-deprotonation versus β-methylation is increased in our system relative to that studied by Paquette.

An alternate strategy for introduction of the requisite methyl group involves cyclopropanation of the carbon−carbon double bond in **6** to yield **13** (Table 1), followed by regioselective reduction to give **7**. Dimethylsulfoxonium methylide ($Me_2S(O)=CH_2$)[10] has been used to cyclopropanate electron-deficient alkenes.[11] In most examples to date, however, tetrasubstituted alkenes cyclopropanated by this method have been activated by the presence of ketone or aldehyde groups,[12] or by two ester or nitrile groups.[13] We are aware of only two reports involving cyclopropanation of a β,β-disubstituted alkene activated by a single α-ester group. In one case, the cyclopropanated adduct **14** was obtained in only 9% yield under unoptimized conditions (eq 3),[14] however, γ-lactones **15a** and **15b**, bearing a disubstituted *exocyclic* α-methylene group, have been cyclopropanated by this method in moderate to good yield (eq 4).[15]

Initial attempts to convert **6** to **13** using $Me_2S(O)=CH_2$ at room temperature were disappointing (entry 1, Table 1). It was found that the methylide decomposed when heated above 60 °C, but heating to 50 °C facilitated

Scheme 3

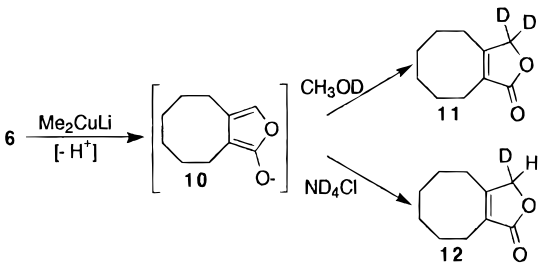
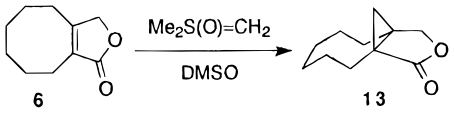


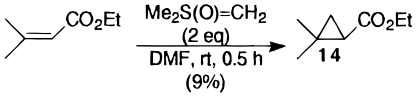
Table 1. Optimization of Cyclopropanation of 2(5*H*)-furanone 6



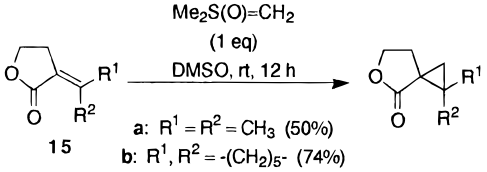
entry	methylide[a] (equiv)	total time (h)	temp (°C)	% conversion (by GC)
1	1.2	2.5	25	0
2	1.2	12	50	21
3	5	11	50	39
4	5	24	50	70
5	10	21	50	86
6[b]	10	21	50	81
	+10	41		90
	+5	62		93

[a] Dimethylsulfoxonium methylide was prepared from $Me_3S^+(O)I^-$ using NaH in DMSO.[10] [b] Additional portions of methylide solution were added to the reaction mixture after the indicated reaction times.

(8) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047−1050.
(9) Lipshutz, B. H. *Tetrahedron Lett.* **1983**, *24*, 127−130.
(10) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.
(11) Gololobov, Y. G.; Nesmeyanov, A. N.; Lysenko, V. P.; Boldeskul, I. E. *Tetrahedron* **1987**, *43*, 2609−2651.
(12) For recent examples, see: (a) Schneider, M. F.; Junga, H.; Blechert, S. *Tetrahedron* **1995**, *51*, 13003−13014. (b) Thielemann, W.; Schafer, H. J.; Kotila, S. *Tetrahedron* **1995**, *51*, 12027−12034. (c) Kumar, P.; Rao, A. T.; Saravanan, K.; Pandey, B. *Tetrahedron Lett.* **1995**, *36*, 3397−3400. (d) Cossy, J.; Furet, N.; BouzBouz, S. *Tetrahedron* **1995**, *51*, 11751−11764. (e) Gustafsson, J.; Sterner, O. *Tetrahedron* **1995**, *51*, 3865−3872. (f) Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* **1994**, *35*, 7217−7220.
(13) For typical examples, see: (a) Yankee, E. W.; Badea, F. D.; Howe, N. E.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 4210−4219. (b) Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972−3975. (c) Annen, K.; Hofmeister, H.; Laurent, H.; Seeger, A.; Wiechert, R. *Chem. Ber.* **1978**, *111*, 3094−3104.
(14) Landor, S. R.; Punja, N. *J. Chem. Soc. (C)* **1967**, 2495−2500.
(15) Minami, T.; Matsumoto, M.; Suganuma, H.; Agawa, T. *J. Org. Chem.* **1978**, *43*, 2149−2153.



eq 3



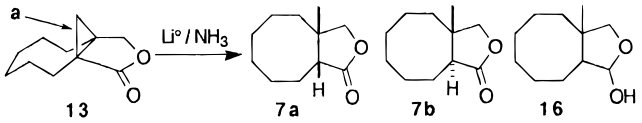
eq 4

cyclopropanation (entry 2). The use of excess methylide and prolonged reaction times (entries 3−5) also improved the overall conversion to cyclopropane **13**; however, little or no additional conversion to product **13** occurred after the reaction had gone to ∼90% conversion, even on addition of a large excess of methylide (entry 6). The crude isolated product of a cyclopropanation reaction that had undergone 74% conversion of **6** to **13** (determined by GC analysis) was resubjected to cyclopropanation reaction conditions using 10 equiv of the methylide. After 19 h at 50 °C, GC analysis showed complete conversion to the desired product. To date, our best results for this reaction have been obtained by using 10 equiv of the methylide in anhydrous DMSO at 45 °C. After 30 h, GC analysis showed 80% conversion to the desired product. The reaction was then worked up, and the crude organic material was resubjected to identical reaction conditions. Complete conversion was effected and the cyclopropyl lactone was isolated and purified in 53% yield.[16] To our knowledge, this is the first synthetically useful cyclopropanation of an 3,4-disubstituted 2(5*H*)-furanone.

Dimethylsulfoxonium methylide is typically generated by deprotonating the corresponding trimethylsulfoxonium chloride or iodide with NaH.[10] All of the above experiments were performed using methylide derived from trimethylsulfoxonium iodide. When the optimized cyclopropanation protocol was repeated using trimethylsulfoxonium chloride *in lieu* of the iodide, it was found that the isolated yield of **13** dropped from 53% to 27%. Given that the iodide salt is also less expensive, this is clearly the precursor of choice. Landor and Punja[14] reported that the use of DMF instead of DMSO as the reaction solvent for similar cyclopropanation reactions resulted in increased yields. In our hands, the cyclopropanation of **6** proceeded equally well in DMF or DMSO.[17]

Previous workers have alluded to the ability of the methylide to deprotonate ketones and enones with enolizable α-protons,[10,18] and we found this to be true for 2(5*H*)-furanone **6**. Treatment of **6** with 1.2 equiv of the methylide for 12 h at rt and then quenching with solid ND_4Cl gave **12**, indicating that deprotonation of **6** is essentially complete under these conditions. Repeating this experiment at 50 °C showed similar deuterium incorporation to yield **12**; however, GC and ^{1}H NMR analysis also showed 10% conversion to cyclopropane **13**. Apparently the same competing γ-deprotonation reaction pathway is occurring here as in the cuprate reactions (*vide supra)* through the intermediacy of furan oxide **10**. Deprotonation appears to be essentially complete at room temperature; however, the small residual concentration of **6** can undergo cyclopropanation at elevated temperatures. Acid−base equilibration then presumably results in regeneration of **6** from **10** which can be consumed via cyclopropanation, eventually resulting in the efficient formation of cyclopropane adduct **13**. The contrasting results observed with γ-lactones **15a** and **15b** can be rationalized by the lower acidity of these substrates; thus cyclopropanation becomes the only available pathway.

Table 2. Optimization of Dissolving Metal Reduction of Cyclopropyl Lactone 13



			ratio of products[a]		
entry	Li (equiv)	temp (°C)	**7a**	**7b**	**14**
1	6.0	−78	1	1	6
2	2.0	−33	2	1	1
3	2.0	−78 to −47	8	2	1
4	2.0	−78 to −55	10	1	0
5	2.0	−78 to −63	16	1	0

[a] The distribution of products was determined by integration of the ^{1}H NMR spectrum of the crude reaction product.

In order for this chemistry to be useful in the context of the aforementioned taxane chemistry, regioselective reduction of cyclopropyl lactone **13** to bicyclic lactone **7** was necessary. Attempts to accomplish this by catalytic hydrogenation were unsuccessful as this cyclopropane was completely unreactive toward hydrogenation under a variety of conditions.[19] It is possible that the cyclopropane ring in **13** is sterically crowded by the eight-membered ring, thus blocking its access to the catalytic surface.

The low steric demands associated with dissolving metal reduction suggested this as an attractive alternate approach for reduction of cyclopropane **13**. It is known[20] that the reduction of conjugated cyclopropyl carbonyl compounds with lithium in liquid ammonia can be achieved regioselectively at the cyclopropane bond that has the maximum overlap with the π-orbital of the carbonyl group. An examination of molecular models clearly showed that reduction of cyclopropyl lactone **13** under these conditions should result in the selective cleavage of bond a (**13** in Table 2), leading to the desired bicyclic lactone **7.** To parallel a published procedure,[21] cyclopropyl lactone **13** was treated with 6 equiv of lithium in liquid ammonia (Table 2, entry 1).

Apparent in the ^{1}H NMR spectrum of the crude product were unreacted starting material and a 1:1 mixture of *cis*- and *trans*-fused cyclopropane reduction products **7a** and **7b**; however, the predominant product, which was subsequently isolated as a 5:1 mixture of two diastereomers in 39% yield by column chromatography, was the cyclic hemiacetal **16**. Trace amounts of other diastereomers of **16** were visible just above the baseline of the ^{1}H NMR spectrum, but these resonances were not readily

(16) We believe that this modest isolated yield is a function of the product isolation efficiency.

(17) Reaction conditions: $Me_2S(O)=CH_2$ (1.2 equiv), 50 °C, 12 h. GC analysis showed 21% conversion to product **13** in both cases.

(18) Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3004−3005.

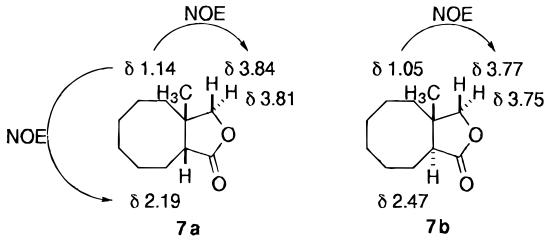
(19) Catalytic hydrogenations were carried out in ethanol, ethyl acetate, or acetic acid in the presence of PtO_2, Pd/C, or Raney nickel. Temperatures as high as 60 °C and hydrogen pressures as high as 1500 psi were employed.

(20) (a) Norin, T. *Acta Chem. Scand.* **1965**, *19*, 1289−1292. (b) Dauben, W. G.; Wolf, R. E. *J. Org. Chem.* **1970**, *35*, 374−378.

(21) Srikrishna, A.; Krishnan, K.; Yelamagged, C. V. *Tetrahedron* **1992**, *48*, 9725−9734.

interpreted. No attempt was made to deduce the relative stereochemistry of these diastereomers.[22]

We considered that avoiding the use of excess reducing agent might preclude reduction of the lactone. This was generally the case when only 2 equiv of lithium were used, although it became evident that the chemoselectivity for this reaction was also highly dependent upon reaction temperature (entries 2−5). Compounds **7a** and **7b** were typically isolated as a 10:1 mixture of diastereomers in excellent yield when the reaction temperature was held below −55 °C (entry 4). Treatment of **13** with 2 equiv of lithium in liquid ammonia/ether at −78 to −63 °C gave a 16:1 mixture of the *cis*- and *trans*-*β*-methyl bicyclic lactones **7a** and **7b** in 92% yield (entry 5). Isolation of pure **7a** was accomplished by recrystallization and the relative stereochemistry of the diastereomers was established by ^{1}H NMR NOE experiments. Specifically, irradiation of the methyl group protons in **7a** (*δ* 1.14)



resulted in an enhancement of the signal at *δ* 2.19, assigned to the proton at the ring juncture, as well as enhancement of one of the lactone methylene proton signals (*δ* 3.84) but not the other (*δ* 3.81). When a 1:1 mixture of diastereomers **7a** and **7b** was similarly irradiated in the ^{1}H NMR spectrum, the results were identical; however, irradiation of the methyl group protons in **7b** (*δ* 1.05) resulted only in enhancement of one of the lactone methylene proton signals (*δ* 3.77). As expected, there was no enhancement of the signal due to the ring juncture proton (*δ* 2.47). Formation of the *cis*-diastereomer of **7a** as the major product from this reaction should be inconsequential in the application of this chemistry to the construction of the taxane ring system. It is well known that the C-3 hydrogen at the taxane BC ring juncture (paclitaxel numbering) is readily epimerized in the presence of a C-2 and/or a C-4 carbonyl group, and that the *trans*-stereochemistry of this ring juncture is often thermodynamically preferred.[23]

Conclusion

An efficient cyclopropanation/reduction protocol for introducing a methyl group at the 4-position of a 3,4-disubstituted 2(5*H*)-furanone has been developed. This methodology should prove useful in introducing the taxane C-8 methyl group, utilizing the 2(5*H*)-furanone functionality which is generated during the closure of the taxane B ring *via* our macrolactonization/transannular aldol condensation strategy. Studies along this direction are currently ongoing. Work is also underway in our laboratory to convert the furanone functionality in **6** to an *α*,*β*-unsaturated ketone containing an intact taxane C ring, where this methylation chemistry might also then be applicable in introducing the taxane C-8 methyl group. Results of these efforts will be reported in due course.

Experimental Section

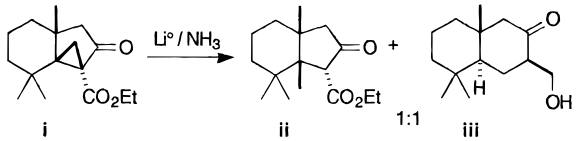
The following solvents and reagents were purified according to standard procedures:[24] THF (distillation from K), ether (distillation from Na/benzophenone), DMSO (vacuum distillation from CaH_2), DMF (vacuum distillation from CaH_2), NH_3 (distillation from Na) and CuI (recrystallization from saturated aqueous KI). All reactions were performed in oven-dried (125 °C) glassware under argon using standard inert atmosphere techniques. Reactions were typically monitored using either TLC on commercial silica plates or GC. Flash column chromatography was performed according to the method of Still, Khan, and Mitra.[25] Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Only major diagnostic IR spectral absorption bands are reported. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and 75 MHz, respectively. ^{1}H NMR NOE experiments were performed at 600 MHz. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA.

4,5,6,7,8,9-Hexahydrocycloocta[*c*]furan-1(3*H*)-one (6). 2(5*H*)-Furanone **6** was prepared according to the literature procedure[5] from cyclooctanone: ^{1}H NMR: *δ* 4.62 (s, 2H), 2.50 (app t, 2H, J = 6.6 Hz), 2.48 (t, 2H, J = 6.5 Hz), 1.81 (m, 2H), 1.69 (m, 2H), 1.54 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 175.3,[26] 161.5, 126.8, 71.5, 26.9, 26.5, 26.0, 25.9, 25.3, 22.1. IR (neat) υ_{max} 2931, 2860, 1749, 1666, 1449, 1020 cm^{-1}.

CH_3OD-Quenched Reaction of 2(5*H*)-Furanone 6 with Me_2CuLi To Yield 3,3-Dideuterio-4,5,6,7,8,9-hexahydrocycloocta[c]furan-1(3*H*)-one (11). Lithium dimethylcuprate was prepared by adding methyllithium (1.3 mL, 1.8 mmol, 5.9 equiv, 1.4 M in ether) dropwise, *via* syringe, to a stirred slurry of CuI (173.7 mg, 0.912 mmol, 3.0 equiv) in anhyd ether (5 mL) that had been precooled to 0 °C. The resulting clear, colorless solution was cooled to −78 °C. A solution of 2(5*H*)-furanone **6** (50.4 mg, 0.303 mmol) in anhyd ether (2 mL) was added dropwise by syringe to the cuprate solution. The reaction mixture was stirred for 1 h at −78 °C and then warmed to −30 °C. CH_3OD (5 mL, 120 mmol, 400 equiv) was added to the reaction mixture which was then warmed to 0 °C over a 5 min period. The reaction mixture was partitioned with water, and the layers were separated. The aqueous layer was extracted with ether. The organic extracts were washed with water until the aqueous washings were neutral. The organic layer was then shaken with brine and dried over anhyd $MgSO_4$. The solution was filtered and condensed *in vacuo* to yield a dark yellow oil identified as **11** (41.2 mg, 82%, 95% deuterium incorporation by ^{1}H NMR): ^{1}H NMR: *δ* 2.50 (t, J = 6.4 Hz, 2H), 2.48 (t, J = 6.6 Hz, 2H), 1.81 (m, 2H), 1.69 (m, 2H), 1.54 (m, 4H). ^{13}C NMR: *δ* 175.3, 161.3, 126.8, 26.8, 26.4, 26.0, 25.9, 25.2, 21.9.[27]

ND_4Cl-Quenched Reaction of 2(5*H*)-Furanone 6 with Me_2CuLi To Yield 3-Deuterio-4,5,6,7,8,9-hexahydro-

(22) In retrospect, it is not surprising that the lactone functionality was reduced. Treatment of *β*-keto ester **i** with lithium in liquid ammonia is known to afford hydrindanone **ii** and decalin **iii**, where cyclopropane reduction is accompanied by reduction of the ester group (ref 21).



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(26) This resonance was not reported in reference 5; instead, a signal at *δ* 150.0 was cited.

(27) The C−D coupling and lack of NOE meant that the CD_2 carbon resonance was not observable above the spectral base line.

cycloocta[*c*]furan-1(3H)-one (12). An ethereal solution of lithium dimethylcuprate (2.39 mmol, 3 equiv) at −78 °C was prepared as described in the previous experiment. A solution of 2(5*H*)-furanone **6** (131.8 mg, 0.793 mmol) in anhyd ether (3 mL) was added by syringe to the cuprate solution. The reaction mixture was warmed to 0 °C over the next 2.75 h at which time solid ND_4Cl (455.1 mg, 7.9 mmol, 10 equiv) was added to the reaction mixture. The reaction mixture was allowed to warm to room temperature over the course of 3 h. The reaction mixture was partitioned with water, and the aqueous layer was extracted with ether. The ether extracts were washed with water and brine and dried over anhyd $MgSO_4$. The solution was filtered and condensed *in vacuo* to yield 116.3 mg of a yellow oil identified as **12**: ^{1}H NMR: δ 4.63 (s, 1H), 2.50 (t, J = 6.5 Hz, 2H), 2.48 (t, J = 6.6 Hz, 2H), 1.81 (m, 2H), 1.69 (m, 2H), 1.54 (m, 4H). ^{13}C NMR: δ 175.3, 161.4, 126.8, 71.5, 26.9, 26.5, 26.0, 25.9, 25.3, 22.1.

10-Oxa[6.3.1]propellan-9-one (13). Dimethylsulfoxonium methylide (150 mmol, 10.0 equiv) in anhyd DMSO (150 mL) was prepared from trimethylsulfoxonium iodide according to literature methods.[10] A solution of 2(5*H*)-furanone **6** (2.50 g, 15.0 mmol) in anhyd DMSO (5 mL) was added by syringe to the clear methylide solution. The reaction mixture was heated to 45 °C. After 30 h, the reaction was allowed to cool to room temperature and was quenched by the addition of 10% aq NH_4Cl (250 mL). This mixture was extracted with ether. The ether extracts were washed with water and brine and dried over anhyd $MgSO_4$. The solution was filtered and condensed *in vacuo* to yield 2.40 g of a yellow oil. ^{1}H NMR analysis of this crude product showed 80% conversion of **6** to **13**. In order to effect complete conversion, the crude product was resubjected to identical reaction conditions for 20 h, when GC analysis showed only the desired product. The reaction was worked up as above to afford a yellow oil (1.97 g). Purification by flash column chromatography (hexanes−ethyl acetate, 5:1) afforded the title compound **13** as a white crystalline solid, mp 66−67 °C (1.43 g, 53%). ^{1}H NMR: δ 4.24 (d, J = 9.1 Hz, 1H), 4.07 (d, J = 9.1 Hz, 1H), 2.56 (dt, J = 15.0, 3.4 Hz, 1H), 2.23 (dt, J = 15.4, 3.8 Hz, 1H), 1.68−1.21 (m, 8H), 1.27 (ddd, J = 15.4, 12.7, 4.7 Hz, 1H), 1.08 (ddd, J = 15.4, 12.1, 3.5 Hz, 1H), 0.96 (d, J = 4.5 Hz, 1H), 0.78 (d, J = 4.5 Hz, 1H). ^{13}C NMR: δ 178.0, 69.4, 30.5, 30.3, 27.0, 26.1, 25.8, 25.7, 25.5, 25.1, 23.5. IR (neat oil): υ_{max} 3025, 2922, 2860, 1760, 1020 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.42; H, 9.02.

ND_4Cl-Quenched Reactions of 2(5*H*)-Furanone 6 with Dimethylsulfoxonium Methylide To Yield 3-Deuterio-4,5,6,7,8,9-hexahydrocycloocta[*c*]furan-1(3*H*)-one (12) and 10-Oxa[6.3.1]propellan-9-one (13). Dimethylsulfoxonium methylide (3.62 mmol, 6.01 equiv) in anhyd DMSO (3.6 mL) was prepared from trimethylsulfoxonium iodide according to the literature method.[10] Each of two round bottom flasks were charged with furanone **6** (100 mg, 0.602 mmol) and the previously prepared methylide solution (0.72 mL, 1.2 equiv). Both flasks were stirred for 12 h, one at rt (A), the other at 50 °C (B). Each reaction was quenched by the addition of ND_4Cl (174 mg, 3.02 mmol, 5.01 equiv). In each case, the reaction mixture was partitioned between ice-water and ether. The aqueous layer was extracted with ether. The organic layers were shaken with brine and dried over anhyd Na_2SO_4. The crude reaction products were analyzed by GC and ^{1}H NMR spectroscopy: reaction A, the monodeuterated furanone **12** was obtained as the sole product; reaction B, a 9:1 mixture of monodeuterated furanone **12** and 10-oxa[6.3.1]propellan-9-one (**13**) was obtained.

9-Hydroxy-1-methyl-10-oxabicyclo[6.3.0]undecane (16). A solution of compound **13** (51.3 mg, 0.285 mmol) in anhyd ether (2 mL) was added by syringe to stirring anhyd liquid NH_3 (20 mL) at −78 °C. Li wire (12 mg, 1.7 mmol, 6.0 equiv) was added to the reaction flask, and after 11 min, a blue solution was observed. After stirring for 2 h at −78 °C, the reaction was warmed to −33 °C and refluxed at that temperature for 1 h. The reaction was then quenched by the addition of excess solid NH_4Cl, dissipating the blue color. After the NH_3 had evaporated, the residue was taken up in water and extracted with ether. The ether extracts were washed with brine and dried over anhyd $MgSO_4$. The solution was filtered and condensed *in vacuo* to yield 52.6 mg of a yellow oil. Purification by flash column chromatography (hexanes−ethyl acetate, 4:1) gave three fractions. **Fraction 1**: 5.3 mg of a colorless oil, identified by ^{1}H NMR analysis as a 2:1 mixture of **13** and **14**. **Fraction 2**: 21.0 mg of a colorless oil, identified as a 5:1 mixture of two diastereomers of **14**. ^{1}H NMR: major diastereomer; δ 5.06 (dd, J = 4.2, 0.9 Hz, 1H), 3.67 (d, J = 8.4 Hz, 1H), 3.48 (d, J = 8.4 Hz, 1H), 2.91 (d, J = 4.5 Hz, 1H), 1.28 (s, 3H), 1.18−1.88 (m, 13H); minor diastereomer; δ 5.61 (app t, J = 5.2 Hz, 1H), 3.59 (d, J = 7.8 Hz, 1H), 3.36 (d, J = 8.1 Hz, 1H), 2.83 (d, J = 5.1 Hz, 1H), 1.18−1.88 (m, 13H), 1.13 (s, 3H). ^{13}C NMR: major diastereomer; δ 110.3, 80.8, 56.2, 42.0, 31.6, 29.42, 29.35, 25.9, 25.3, 24.8, 21.0; minor diastereomer; δ 101.6, 78.4, 52.2, 43.6, 31.4, 29.8, 29.4, 25.9, 25.3, 24.8, 21.0. IR (neat): υ_{max} 3390, 2921, 2856, 1469, 1442, 1044 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.57; H, 11.08. **Fraction 3**: 5.0 mg of an unidentified, colorless oil.

1-Methyl-10-oxabicyclo[6.3.0]undecan-9-one (7). A solution of compound **13** (200.0 mg, 1.11 mmol) in anhyd THF (5 mL) was added by syringe to cold (−78 °C) stirring anhyd liquid NH_3 (50 mL). Li wire (15.5 mg, 2.23 mmol, 2.01 equiv) was added to the reaction flask, imparting a blue color after 10 min of vigorous stirring. The reaction temperature was allowed to rise to −55 °C over a 3 h period at which time the color had faded to a light blue. The reaction temperature was held at −55 °C for 48 min as the remaining color dissipated. The reaction was quenched by the addition of solid NH_4Cl (119.8 mg, 2.01 equiv, 2.23 mmol), and the NH_3 was allowed to evaporate. The remaining solvent was removed *in vacuo*, and the residue was partitioned between water and ether. The aqueous layer was extracted with ether, and the ether extracts were washed with water and brine and dried over anhyd $MgSO_4$. The solution was filtered and condensed *in vacuo* to yield 197.6 mg (98%) of a white crystalline solid, mp 34.5−37.0 °C. ^{1}H NMR analysis showed that the crude product contained a 10:1 mixture of **7a** and **7b**. This material was recrystallized from pentane at −5 °C to give 84.3 mg (42%) of a white crystalline solid, mp 52.5−53.5 °C, identified as **7a**: ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.84 (d, J = 8.4 Hz, 1H), 3.81 (d, J = 9.0 Hz, 1H), 2.18 (d, J = 10.2 Hz, 1H), 1.99−1.94 (m, 1H), 1.87−1.75 (m, 4H), 1.72−1.60 (m, 2H), 1.45−1.37 (m, 2H), 1.28 (dt, J = 14.4, 3.6 Hz, 1H), 1.21−1.06 (m, 2H), 1.13 (s, 3H). ^{13}C NMR: δ 182.3, 78.5, 52.7, 41.0, 31.8, 28.7, 27.0, 25.4, 24.5, 24.2, 24.1. IR (neat): υ_{max} 2926, 2858, 1773, 1466, 1446 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.29; H, 10.11. The mother liquor was condensed *in vacuo* to yield 97.3 mg (48%) of a yellow oil, shown by ^{1}H NMR analysis to contain a 4:1 mixture of **7a** and **7b**. **7b** (diagnostic resonances only): ^{1}H NMR: δ 3.77 (d, J = 8.6 Hz, 1H), 3.75 (d, J = 8.6 Hz, 1H), 2.47 (dd, J = 3.0, 11.0 Hz, 1H), 1.05 (s, 3H).

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