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Comparative reductive desymmetrization of 2,2-disubstituted-cycloalkane-1,3-diones

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Abstract

Reductive desymmetrization of 2-methyl-2-substituted-cycloalkane-1,3-diones can be effected using either $NaBH_4$ in DME or lithium tri-*tert*-butoxyaluminum hydride (LTBA) in THF at −60 °C. The former is a new approach that offers slightly greater diastereoselectivity in the reduction of 2,2-disubstituted-cyclopentane-1,3-diones while LTBA is superior with 2,2-disubstituted-cyclohexane-1,3-diones. Both conditions minimize subsequent reduction to diols thereby furnishing high yields of 1,3-ketols. Particularly rapid monoreductions are observed with 2-methyl-2-nitroethylcyclopentane-1,3-dione and 2-cyanoethyl-2-methylcyclopentane-1,3-dione when treated with $NaBH_4$ in DME at −60 °C. As expected, diastereoselectivity varies considerably with the substitution at C-2.
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1. Introduction

The monoreduction of 2,2-disubstituted-cycloalkane-1,3-diones is an important protocol for the synthesis of terpenoid natural products and substrates used to establish new synthetic methods. Although several alternatives now exist for the enantioselective monoreduction of such diones,[1] the cost and inconvenience of these approaches is unwarranted for applications where a stereospecific modification, e.g., ring fragmentation that requires only appropriate relative configuration or an elimination of the newly formed chirality center in the 2,2-disubstituted-1,3-ketols, is desired.

Few methodological studies have been published regarding the diastereoselective reductive desymmetrization of 2,2-disubstituted-cyclic-1,3-diones. Kuo et al. first employed lithium tri-*tert*-butoxyaluminum hydride (LTBA) to this end in excellent reported yield but poor diastereoselectivity in their synthesis of estrone.[2] The Molander and Mori groups both exploited $NaBH_4$ in monoreductions en route to substrates used to establish new methods for medium-size carbocycle synthesis.[3] However, reported diastereoselectivities were poor and specific information regarding reaction conditions is sparse. Others have used $NaBH_4$ in protic media with unsatisfactory results.[4] More recently, both Burnell and Lee monoreduced sterically biased 2,2-disubstituted-cyclopentane-1,3-diones with Et_3SiH in concentrated TFA over 10 h.[5] Although these reactions occurred in excellent reported yields and diastereoselectivities, such harsh conditions are not compatible with many substrates. Herein we highlight a mild, inexpensive method for the diastereoselective desymmetrization of 2,2-disubstituted-cycloalkane-1,3-diones using $NaBH_4$ in DME. We also provide the first extensive investigation into the capacity of LTBA to effect the diastereoselective monoreduction of carbocyclic-1,3-diones bearing disparate substituents at C-2.

2. Synthesis of 2,2-disubstituted-cycloalkane-1,3-diones

Surveyed cyclic 2,2-disubstituted-1,3-diones were prepared from commercially available diones **1** and **7** by published procedures (Scheme 1). Allyl derivatives **2** and **8** were accessed via Tsuji–Trost allylation[6] or allylic substitution[7] then converted to the corresponding *n*-propyl analogs **3** and **9** via catalytic hydrogenation. Compounds **4** and **10** were accessed by

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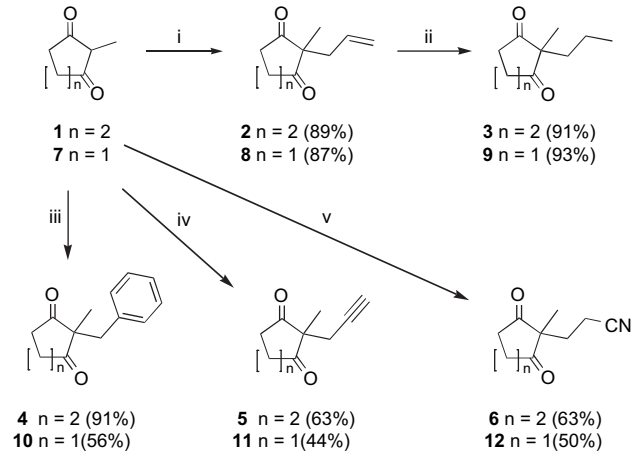
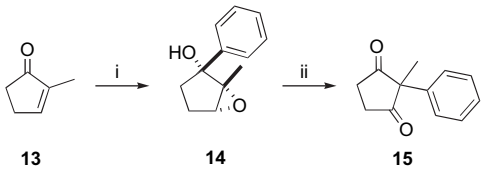


Scheme 1. (i) $Pd(OAc)_2$ (cat.), PPh_3 (cat.), THF, rt, 25 min, then allyl methylcarbonate, rt; (ii) Pd/C (cat.), H_2, rt, 2 h; (iii) LiI, DBU, MeCN, rt, 1 h, then BnBr, reflux; (iv) 1 N NaOH, $BrCH_2CCH$, 60 °C; (v) H_2CCHCN, Et_3N, reflux.

active methylene enolate C-alkylation using benzyl bromide,[8] and substrates **5** and **11** were similarly prepared with propargyl bromide.[7,9] Meanwhile, Michael addition to acrylonitrile in refluxing triethylamine furnished cyanoethyl diones **6** and **12**.[7]

We also prepared 2-methyl-2-phenyl-cyclopentane-1,3-dione (**15**) from 2-methylcyclopentenone (**13**) (Scheme 2). A



Scheme 2. (i) PhBr, *t*-BuLi (2 equiv), −78 °C, then *m*-CPBA, DCM, 0 °C; (ii) $BF_3 \cdot OEt_2$, DCM, −40 °C, 52% over 3 steps, then PCC, DCM, 22 °C, 1 h, 88%.

1,2-addition to phenyllithium followed by *m*-CPBA epoxidation of the ensuant allylic alcohol provided epoxycarbinol **14**. Semipinacol rearrangement[10] of **14** mediated by $BF_3 \cdot OEt_2$ and subsequent oxidation furnished substrate **15**.

3. Results and discussion

3.1. Monoreductions using $NaBH_4$ in DME

In considering an economical method for effecting the monoreduction of cyclic 2,2-disubstituted-1,3-diones, we reasoned that the marginal successes reported using $NaBH_4$ could be improved by moderating the reactivity of the reductant. Brown reported that 1,2-dimethoxyethane retards the rate of borohydride-mediated reductions compared to reactions

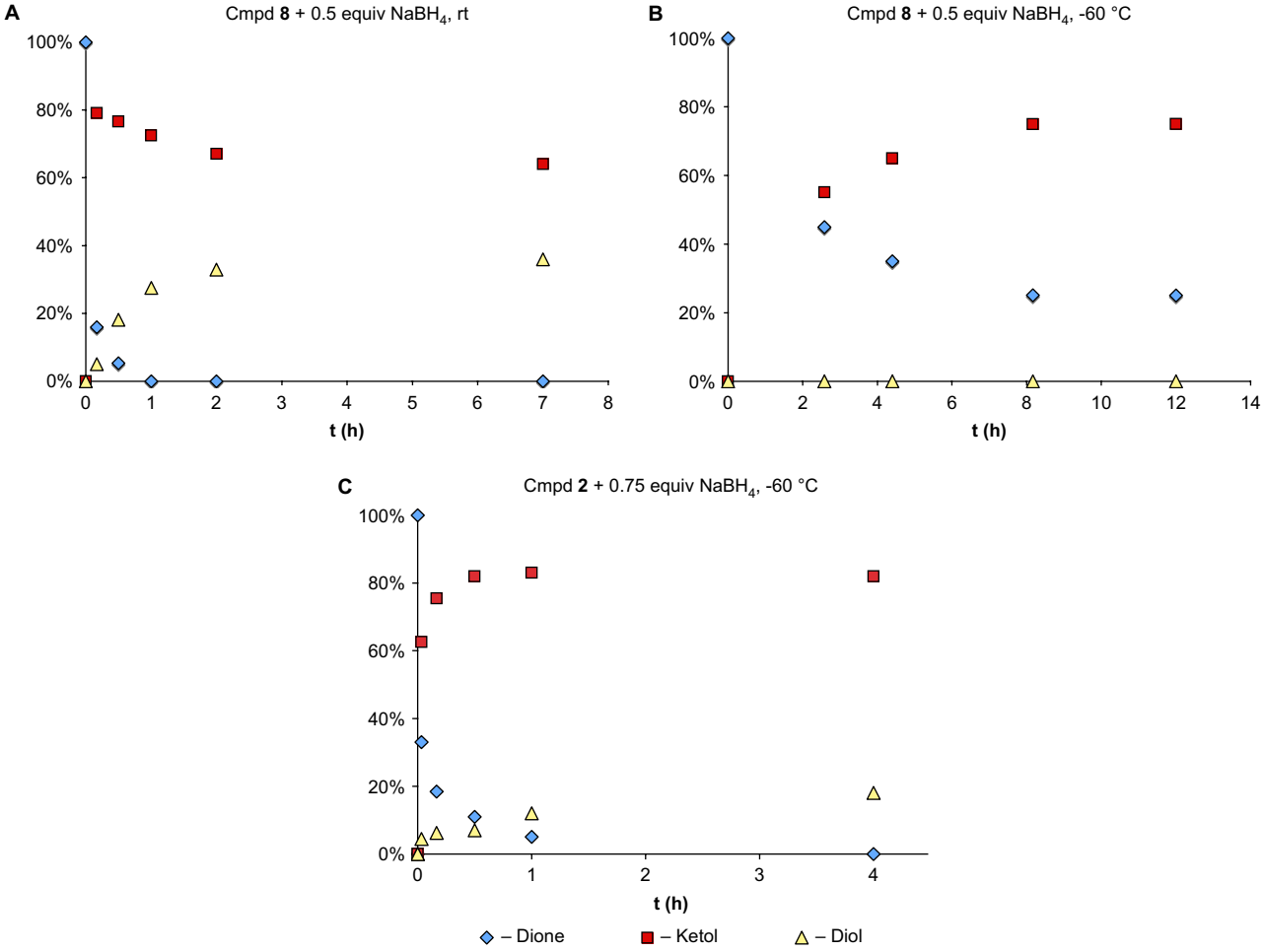


Figure 1. Product distribution analysis over time in the reductions of **8** and **2** with $NaBH_4$ in DME.

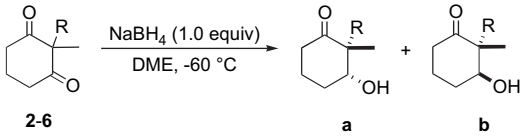


Figure 2. Monoreduction of 2,2-disubstituted-cyclohexane-1,3-diones using 1.0 equiv of $NaBH_4$ in DME at −60 °C.

conducted in lower alcohols.[11] Given the reportedly poor ability of $NaBH_4$ to reduce ketones in DME, we were curious to determine whether the harnessed reactivity of $NaBH_4$ in the aprotic solvent could lead to controlled monoreduction of disparately substituted 2,2-disubstituted-cyclic-1,3-diones. The affordability, simplicity, and functional group compatibility of such a method would offer obvious benefits.

We began our investigation by testing the ability of $NaBH_4$ in DME to effect the monoreduction of **8**. At 23 °C, complete consumption of the starting material was witnessed within 1 h using 0.5 equiv of $NaBH_4$. However, at this temperature, nearly 30% of the desired 1,3-ketol was also reduced to the diol within 60 min (Fig. 1A). Decreasing the reaction temperature to −60 °C afforded superior control of the bis-reduction with <5% of diol formation even after 12 h (Fig. 1B). Increasing the concentration of $NaBH_4$ from 0.5 to 1.0 equiv led to greater conversion and reaction rates but was accompanied by increasing amounts of diol formation and a notable decline in diastereoselectivity. For these reasons, we elected to use 0.5 equiv of $NaBH_4$ in −60 °C DME as our optimal reaction conditions.

Similar results were found when evaluating substrate **2**, although with the cyclohexanedione homolog, ketol formation plateaued within 1 h even at −60 °C (Fig. 1C). Unlike with the cyclopentanedione substrates, the concentration of the diol continually increased with time, suggesting that the monoreduction should be terminated at 30 min to afford optimal results. We also found that employing up to 1.0 equiv of $NaBH_4$ during these reductions enhanced the percentage conversion to the desired ketols without a significant increase in the rate of diol formation.

Encouraged by the results of our optimization studies, we applied the newly devised conditions to variably substituted substrates **2**–**6** to ascertain the level of substrate-controlled diastereoselectivity furnished during the monoreductions (Fig. 2). The highest isolated yields were attained by treating the disubstituted-diones with 1.0 molar equivalent of $NaBH_4$ in DME at −60 °C for 30–60 min (reaction progress monitored by TLC and optimized after multiple runs). In all cases, the diones were quickly reduced giving good combined isolated yields of diastereomeric ketols (Table 1). The results feature interesting levels of diastereoselectivity for the favored *cis*-stereoisomer, with benzyl-substituted compound **4** offering the highest stereocontrol (dr=8.6:1).

Treatment of the substituted cyclopentanediones **8**–**12** and **15** at −60 °C with 0.5 molar equivalents of $NaBH_4$ in DME also produced high yields of ketols (Fig. 3). Routine monitoring of reaction progress by TLC indicated that the diones were consumed within 24 h. The decreased rate in $NaBH_4$ reduction of cyclopentanones relative to cyclohexanone homologs has been documented previously.[12] Given the sluggish reduction

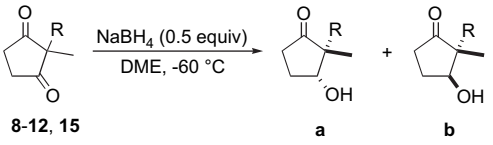
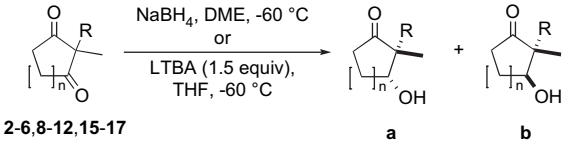


Figure 3. Monoreduction of 2,2-disubstituted-cyclopentane-1,3-diones using 0.5 equiv of $NaBH_4$ in DME at −60 °C.

Table 1
Monoreductions of 2-methyl-2-substituted-cycloalkane-1,3-diones



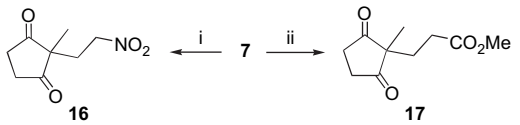
Entry	Compd	*n*	Substituent (R)	$NaBH_4$, DME, −60 °C				LTBA, THF, −60 °C	
				Equiv	Time (h)	dr[a] (**a**/**b**)	Yield[b] (%)	dr[a] (**a**/**b**)	Yield[b] (%)
1	**2**	2	Allyl	1.0	0.5	3.3:1	82	5.0:1	87
2	**3**	2	Propyl	1.0	0.5	4.3:1	81	5.9:1	91
3	**4**	2	Benzyl	1.0	0.5	8.6:1	81	12:1	95
4	**5**	2	Propargyl	1.0	0.5	1.4:1	77	1.4:1	77
5	**6**	2	Cyanoethyl	1.0	0.5	1.1:1	85	1.1:1	85
6	**8**	1	Allyl	0.5	20	3.3:1	86	2.2:1	85
7	**9**	1	Propyl	0.5	20	5.1:1	82	4.0:1	93
8	**10**	1	Benzyl	0.5	24	4.9:1	83	3.9:1	89
9	**11**	1	Propargyl	0.5	24	1.0:1	79	1.3:1	83
10	**12**	1	Cyanoethyl	0.5	2	1:1.1	82	1:1.2	91
11	**15**	1	Phenyl	0.5	20	16:1	93	11:1	95
12	**16**	1	Nitroethyl	0.5	3	1:1.4	76	1:1.4	88
13	**17**	1	Methyl propanoate	0.5	17	1.6:1	80	1.9:1	82

[a] Determined by ^1H NMR analysis of crude reaction mixture and NOE difference spectroscopy of purified materials.
[b] Isolated yield of purified combined ketols **a** and **b**.

rates for **8**–**11** and **15**, we were surprised to find that dione **12** was largely consumed within 2 h. Analysis of reaction products over 22 h showed that unlike in the reduction of **8** (Fig. 1B), the ketol from **12** was continually reduced to the diol as the reaction proceeded (Fig. 4A).

Intrigued by the rate enhancement displayed by **12** relative to the other analogs, we decided to evaluate two additional substrates bearing electron-attracting substituents attached with an ethyl tether to find if they offered similar reduction rates and diastereoselectivities. Compound **16** was prepared by reacting **7** with nitroethylene and catalytic quantities of $P(Bu)_3$[13] while methyl ester **17** was prepared via a Michael addition between **7** and methyl acrylate (Scheme 3).[7]

Subjecting diones **16** and **17** to our optimized conditions provided unexpected results (Table 2). Compound **17** was slowly consumed over 20 h (Fig. 4C), reminiscent of the reactivity displayed by the majority of the examined cyclopentanedione substrates. However, **16** (Fig. 4B) exhibited a reduction rate analogous to that seen with **12**. Presently we have no explanation for this rate enhancement. The distance of the nitro and cyano groups from the carbonyl carbon precludes activation through carbonyl polarization. In addition, the significantly slower reduction rate displayed by **17**, which bears a methyl ester, disfavors a general effect in substrates featuring a tethered



Scheme 3. (i) H_2CCHNO_2, cat. PBu_3, MeCN, rt 20 h; (ii) H_2CCHCO_2Me, Et_3N, reflux.

electron withdrawing substituent. Displacement of a hydride and coordination to the cyano and nitro groups in DME seems unlikely to promise a marked rate increase, as the resulting hydride addition would involve an eight-member transition state and little kinetic advantage over the intermolecular pathway. Curiously, compounds **12** and **16** were also the only substrates to display selectivity, albeit modest, for *trans*-ketols.

Table 2
Monoreduction of diones **16** and **17** using 0.5 equiv of $NaBH_4$ in DME at −60 °C

Entry	Substrate	Selectivity (**a**/**b**)[a]	Isolated yield[b] (%)
1	**12**	1:1.1	82
2	**16**	1:1.6	80
3	**17**	1.4:1	76

[a] Determined by ^1H NMR analysis of crude reaction mixture and ^1H NOE difference spectroscopy of purified materials.
[b] Isolated yield of purified combined ketols **a** and **b**.

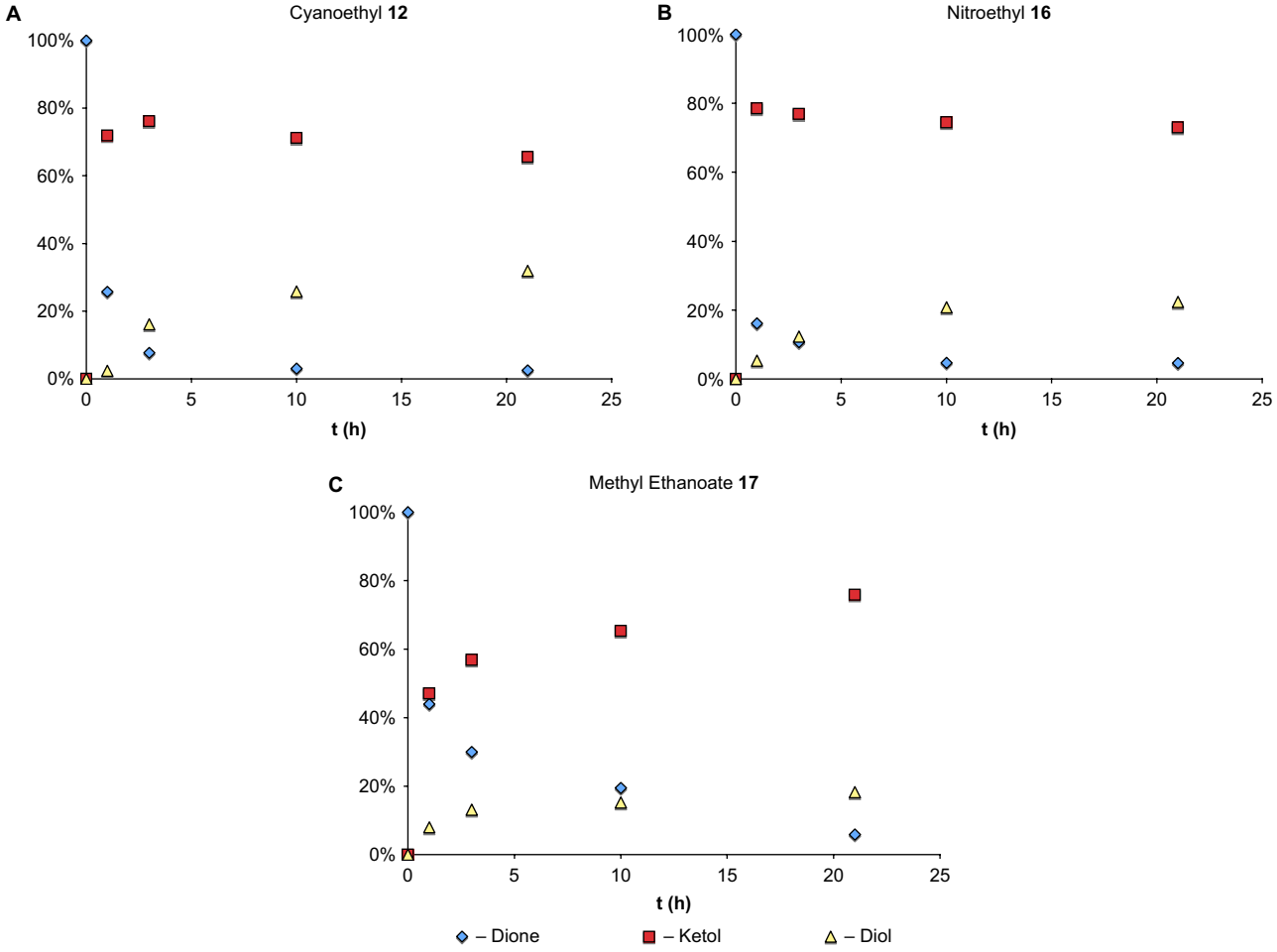


Figure 4. Product distribution analysis over time in the reductions of **12**, **16**, and **17** using $NaBH_4$ (0.5 equiv) in DME at −60 °C.

Excellent stereocontrol is afforded by substrate **15** and reasonable levels are exhibited by **9** and **10**, despite the apparent disparity in steric volume of the attached substituents. All other substrates furnished a minimal preference for generation of the respective *cis*-diastereomers except for **12** and **16**, as noted.

Electron density surfaces onto which the absolute value of the LUMO is plotted (i.e., LUMO maps) have been used to explain the stereoselectivity of carbonyl addition reactions.[14] The LUMO maps reveal both the molecular van der Waals surface and the positions most susceptible to nucleophilic attack (blue regions). The surfaces readily account for facial selectivity among similar systems, and these theoretical results have shown good correlation with experimental findings.

We elected to construct LUMO maps for compounds **3**, **5**, **9**, and **16** (Fig. 5). These compounds were selected because of their steric similarities but disparate facial selectivities during the experimental monoreductions. A conformational search was conducted using the semiempirical PM3 method[15] and then a single-point energy LUMO map was established for the lowest energy ground-state conformer using an HF 6-31G* basis set.[14a]

Examination of the LUMO maps for structures **9** (Fig. 5A) and **16** (Fig. 5B) provides a gratifying rationalization for the observed diastereoselectivities in the reduction of these substrates. The planar face of **9** displaying the methyl substituent (right structure) shows a clear preference (deep blue at carbonyl carbons) for hydride addition relative to the opposite face bearing the *n*-propyl group (left structure). A possible electronic (steric) repulsion (red-orange of the propyl group) is also evident in the leftmost compound. Conversely, both faces of **16** show similar electronic and steric susceptibilities to hydride addition, thereby reflecting little facial differentiation. The electronic and steric information highlighted by these LUMO maps is in excellent agreement with the experimental observations.

The LUMO map of the pseudo-chair equatorial (Fig. 5C right) and axial (Fig. 5C left) faces of **3** displays a clear electronic preference for hydride approach from the axial face, leading to the *cis*-ketol. However, a similar preference is indicated by the LUMO map of **5**, despite that substrate's poor experimentally observed diastereoselectivity. It is important to recognize that factors other than those reflected in LUMO maps affect facial selectivity, especially with the cyclohexane-1,3-diones, including **5**. Depending upon the substrate and the precise reaction conditions, transition state position, steric and torsional effects related to product-development control, the steric impact of the axial hydrogen at C-5 (substrates **2**–**6**), and conformational isomerization are also subtle or major contributors involved in facial selectivity.[12b,16] The latter factor may be particularly relevant to substrates **2**, **3**, **5**, and **6** where conformational isomerization may occur even at −60 °C leading to higher energy, more reactive conformers that are susceptible to hydride addition (Curtin–Hammett systems).

If this is true, drawing conclusions from analysis of the lowest energy conformers of these structures is misleading. As such, collaborative theoretical studies are planned both to gain insight into the stereocontrol exhibited by the substrates examined and to explain the marked rate enhancements offered by **12** and **16** in DME.

3.2. Monoreductions using LTBA in THF

Given our observations in the monoreductions using $NaBH_4$ in DME at reduced temperature, we proceeded to evaluate the ability of lithium tri-*tert*-butoxyaluminum hydride (LTBA) to furnish ketols from substrates **2**–**6**, **8**–**12**, and **15**–**17**. This would not only offer a comparative measure of the performance of $NaBH_4$ in DME but also provide the first extensive investigation concerning the capabilities of LTBA to

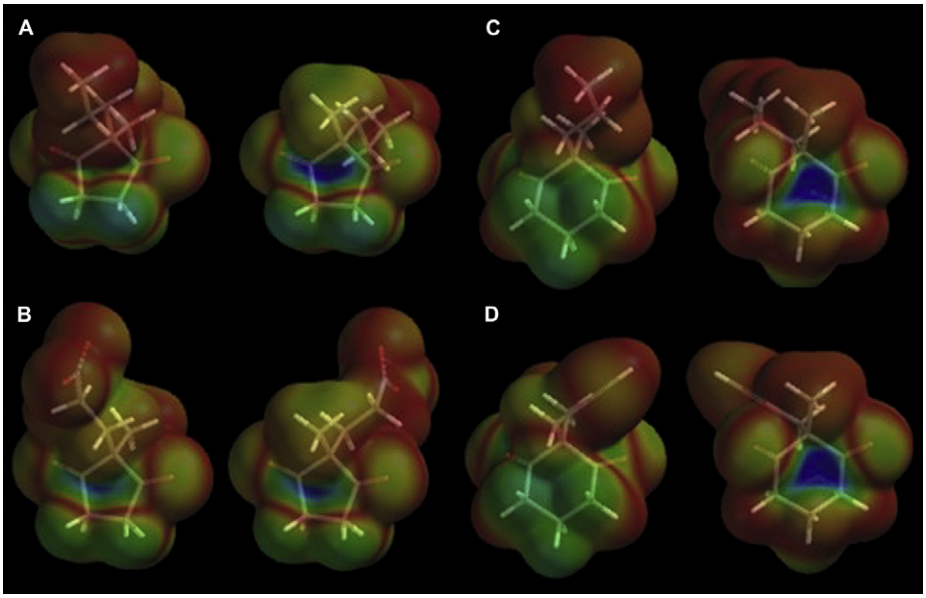


Figure 5. LUMO maps of each face of substrates A=**9**, B=**16**, C=**3**, and D=**5**. The methyl group is projected backward in the leftmost structure of each pair (A–D) and forward in each rightmost structure. Regions shaded in blue reflect areas of maximum value in the LUMO (i.e., most electron deficient regions) and regions in red represent areas of minimal value.

Table 3
Optimization of monoreduction of diones **4** and **10** using LTBA

Entry	Dione	LTBA (equiv)	T (°C)	t (h)	Ketol selectivity[a]	Conversion[a] (%)
1	**4**	1.1	rt	0.5	5.0:1	88
2	**4**	1.1	−20	2	5.4:1	82
3	**4**	1.1	−60	2	9.8:1	74
4	**4**	1.5	−60	2	12:1	95
5	**10**	1.1	rt	0.5	3.2:1	86
6	**10**	1.1	−20	2	3.3:1	87
7	**10**	1.1	−60	2	3.4:1	76
8	**10**	1.5	−60	2	3.9:1	89

[a] Determined by ^{1}H NMR analysis of crude reaction mixture.

monoreduce variably substituted cyclic 1,3-diones. Concerned that the bulky *tert*-butoxy ligands on LTBA might retard the desired reduction of substrates bearing large substituents, we elected to examine benzyl substrates **4** and **10** in our optimization studies. The results are summarized in Table 3.

The optimization studies highlighted an increase in diastereoselective formation of *cis*-ketols with decreasing temperature (compare entries 2 and 3). Although this effect was minor with dione **10**, the results were pronounced with **4**, presumably due to decreased conformational isomerization at low temperature. Unlike the monoreductions with $NaBH_4$ in DME, all reactions involving LTBA were completed within 2 h independent of ring size. We also found that conducting the reactions at −60 °C mandated employment of 1.5 equiv of LTBA to provide desired levels of conversion.

Implementing LTBA in THF at −60 °C gave consistently high yields with all substrates evaluated (Table 1). An advantage of using LTBA for reductive desymmetrization is that subsequent ketol reduction is not observed with any evaluated substrates. This observation corroborates reported results for other dione monoreductions involving the reagent.[2,5b,17] As expected, LTBA displays greater stereoselectivity in the monoreductions of **2**–**6**; the reagent's propensity for axial attack in the reduction of cyclohexanones is superior to that of $NaBH_4$.[18] However, we were surprised to find that the $NaBH_4$/DME protocol afforded enhanced diastereoselectivity in the monoreduction of the cyclopentane-1,3-dione derivatives. Perhaps the reduced reactivity of $NaBH_4$ in DME affords greater selectivity toward these rigid diones.

4. Conclusions

A new approach to the reductive desymmetrization of 2,2-disubstituted-cycloalkane-1,3-diones using $NaBH_4$ in DME at −60 °C shows yields and levels of stereocontrol comparable to those found using LTBA. The $NaBH_4$ in DME approach offers slightly greater facial selectivity in the monoreduction of 2,2-disubstituted-cyclopentane-1,3-diones while LTBA is superior with 2,2-disubstituted-cyclohexane-1,3-diones. Both conditions minimize subsequent reduction to diols thereby furnishing high yields of 1,3-ketols. This comparative study is the first of its kind with this popular class of diones and provides important data for the longstanding campaign to better understand and predict the reactivity and selectivity of hydride-based additions to carbonyl compounds.

5. Experimental

5.1. Molecular modeling

Molecular modeling was conducted using SPARTAN'04 v.1.0.1 (Wavefunction Inc., Irvine, CA, 2003). A ground-state conformer distribution search was conducted on compounds **3**, **5**, **9**, and **16** with the PM3 method.[15] The lowest energy conformers were submitted to single-point energy calculations using the Hartree–Fock 6-31G* basis set. The calculated absolute value of the LUMO was plotted onto the electron density surface (0.002 e/au^3) of each structure to produce the LUMO maps shown in Figure 5.

5.2. General information

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium/benzophenone ketyl radical under argon. 1,2-Dimethoxyethane (DME) was purchased from Aldrich (99.8%), shipped in a SureSeal bottle and used as received. Dichloromethane (DCM) was distilled over CaH_2. Sodium borohydride was purchased from Sigma and lithium tri-*tert*-butoxyaluminum hydride (LTBA) (93–98%) was purchased from Acros and used as received. Starting materials **1** and **7** were purchased from Aldrich, and enone **13** was purchased from SAFC. Alkyl lithium reagents were titrated with 2,5-dimethoxybenzylalcohol (Aldrich) in anhydrous THF immediately before use.[19] Air sensitive materials were handled using standard anoxic transfer techniques employing argon.

Proton magnetic resonance spectra (^{1}H NMR) were recorded at either 360 or 500 MHz. Carbon magnetic resonance spectra (^{13}C NMR) were recorded on spectrometers operating at either 90 or 125 MHz. Nuclear Overhauser enhancement (NOE) difference spectroscopy experiments were performed on a 500 MHz spectrometer. Infrared spectroscopy data (IR) were recorded on a Jasco FT/IR-4100. High-resolution mass spectrometry (HRMS) was performed on an AutoSpec-Ultima NT. Flash column chromatography was conducted using Silicycle silica gel (230–400 mesh). TLC visualization was achieved by ultraviolet light (254 nm), I_2 vapors, acidic *p*-anisaldehyde or vanillin stain. Temperature for monoreduction experiments was controlled using an immersion cooler (NESLAB CC-100) or a $CHCl_3/CO_2$ bath.

Compounds **2** and **8**,[6,7] **4** and **10**,[8] **5** and **11**,[9] **6** and **12**[7] were prepared according to known procedures starting from **1** and **7**, respectively.

5.3. Preparation of 2-methyl-2-phenyl-1,3-cyclopentanedione (*15*)

5.3.1. (±)-2,3-Epoxy-2-methyl-1-phenylcyclopentan-1-ol (*14*)

A solution of freshly distilled bromobenzene (2.1 mL, 20 mmol) and diethyl ether (100 mL) was treated with 1.5 M *tert*-butyl lithium (30 mL, 45 mmol) at −78 °C dropwise via

cannula. Upon transfer of the reagent, the orange solution was allowed to warm to rt for approximately 30 min then cooled to −78 °C. Compound **13** (1.96 mL, 20 mmol) was introduced to the reaction mixture dropwise over 15 min via addition funnel. After stirring for 10 min, the solution was removed from the −78 °C bath and quenched by slow addition of saturated NH_4Cl solution (25 mL). Upon an initial separation, the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were then washed with brine (1×25 mL), dried ($MgSO_4$), and concentrated to give a yellow oil. Purification by flash chromatography (9:1 hexanes/EtOAc) removed major impurities but left traces of unidentified compounds.

The recovered semipure carbinol (3.21 g, 16.9 mmol) was diluted in DCM (40 mL) and cooled to −78 °C. In a separate vessel, 70–77% solid *m*-chloroperoxybenzoic acid (5.38 g, ~23 mmol) was dissolved in DCM (31 mL) at 40 °C. The resultant peroxy acid solution was transferred to the cold carbinol dropwise via cannula. The reaction mixture was allowed to warm to rt then quenched after 3 h by slow addition of saturated aqueous $NaHCO_3$ (20 mL). The phases were separated, and the aqueous layer was extracted with DCM (3×25 mL). The combined organic layers were then washed with brine (1×25 mL), dried ($MgSO_4$), and concentrated to give a yellow oil, which was purified by flash chromatography (9:1 hexanes/EtOAc) to give 3.60 g (18.9 mmol) of the desired epoxide **14** as a white solid. The material was sufficiently pure to use directly in the next reaction. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45–7.28 (m, 5H, Ar), 3.64 (s, 1H), 2.34 (s, 1H), 2.27–2.23 (m, 1H), 2.08–1.98 (m, 1H), 1.90–1.85 (m, 1H), 1.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.1, 128.4, 127.0, 124.4, 82.0, 69.3, 65.0, 38.9, 26.7, 12.7; IR (thin film, cm^{-1}): 3475, 3084, 3058, 3026, 2975, 2932, 2860, 1493, 1450, 1375, 1200, 764, 703; HRMS (EI): calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1001.

5.3.2. *trans*-(±)-3-Hydroxy-2-methyl-2-phenylcyclopentanone

Epoxide **14** (3.60 g, 18.9 mmol) was dissolved in DCM (95 mL) then cooled to −40 °C. To this solution was added $BF_3\cdot OEt_2$ (4.8 mL, 38 mmol) slowly causing the reaction mixture to turn from yellow to deep red. After 35 min, the starting material was consumed (TLC), and the reaction was quenched by the addition of 40 mL of H_2O. The phases were separated, and the aqueous layer was extracted with DCM (3×20 mL). The combined organic layers were washed with brine (1×25 mL) and dried ($MgSO_4$). Upon concentration, the crude oil was purified by flash chromatography (7:3 hexanes/EtOAc) to afford the title compound as a cloudy, colorless oil (1.96 g, 10.3 mmol, 52% over 3 steps). ^{1}H NMR (360 MHz, $CDCl_3$): δ 7.34–7.19 (m, 5H), 4.58 (t, 1H, J=4.7 Hz), 2.60–2.50 (m, 1H), 2.40 (br s, 1H), 2.37–2.27 (m, 1H), 2.16–2.06 (m, 1H), 1.95–1.86 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 219.4, 141.9, 128.8, 127.1, 126.5, 78.2, 58.9, 35.2, 27.5, 17.6; IR (thin film, cm^{-1}): 3442, 2972, 2926, 1735, 734, 701; HRMS (EI): calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1001.

5.3.3. 2-Methyl-2-phenyl-1,3-cyclopentanedione (*15*)

To a solution of *trans*-(±)-3-hydroxy-2-methyl-2-phenylcyclopentanone (954 mg, 5.01 mmol) and DCM (17 mL) was added approximately 2 g of activated 4 Å molecular sieves. The solution was cooled to 0 °C and pyridium chlorochromate (2.699 g, 12.5 mmol) was added portionwise over 5 min. When the starting material was consumed (TLC, ~10 h), the reaction was diluted with diethyl ether (5 mL) and DCM (5 mL) followed by the addition of Celite. The solution was stirred at rt for 1 h then the contents of the flask were filtered over a pad of Celite. The filtrate was then concentrated to give a brown oil, which was purified by flash chromatography (8:2 hexanes/EtOAc) to afford **15** as a clear yellow oil (830 mg, 4.41 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36–7.21 (m, 5H), 2.96–2.85 (m, 2H), 2.79–2.68 (m, 2H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.1, 137.0, 129.4, 128.1, 126.4, 62.1, 35.3, 19.9 (CH_3); IR (thin film, cm^{-1}): 2930, 1724, 749, 699; HRMS (EI): calcd for $C_{12}H_{12}O_2$ $[M]^+$ 188.0837, found 188.0844.

5.4. 2-Methyl-2-(2-nitroethyl)-1,3-cyclopentanedione (*16*)

To an oven-dried 125 mL RBF was added 2-methyl-1,3-cyclopentanedione (**7**, 2.02 g, 18.0 mmol) and dry acetonitrile (35 mL). To this solution was added freshly distilled nitroethylene[20] (2.04 g, 35.7 mmol) followed by the slow addition of tributylphosphine (440 mL, 1.76 mmol) at rt. The reaction was stirred for 20 h at which point the mixture was concentrated and purified by flash chromatography (7:3 hexanes/EtOAc) to afford 1.48 g (7.99 mmol, 44%) of the title compound as an orange-yellow oil. ^{1}H NMR (360 MHz, $CDCl_3$): δ 4.41 (t, 2H, J=6.8 Hz), 2.95–2.76 (m, 4H), 2.33 (t, 2H, J=6.8 Hz), 1.19 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ 214.1, 70.7, 54.0, 34.5, 29.6, 21.9; IR (thin film, cm^{-1}): 3466, 2976, 2931, 2875, 1764, 1719, 1639, 1552; HRMS (EI): calcd for $C_8H_{11}NO_4$ $[M]^+$ 185.0688, found 185.0686.

5.5. Monoreduction experimental procedures

5.5.1. General procedure for $NaBH_4$/DME-mediated reductions

A solution of 2,2-disubstituted-cycloalkane-1,3-dione (0.5 mmol) in DME (1 mL) was cooled to −60 °C for 1 h under argon, then $NaBH_4$ (9 mg, 0.25 mmol) was added to the reaction mixture in one portion. The reaction was stirred at −60 °C until judged complete (TLC) at which point it was quenched with 1 N HCl (1 mL). The mixture was diluted with EtOAc, the phases were separated, and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organics were washed with brine (1×10 mL), dried ($MgSO_4$), and concentrated to afford a crude oil that was examined by ^{1}H NMR spectroscopy then purified by flash chromatography.

5.5.2. General procedure for reductions using lithium tri-tert-butoxyaluminum hydride (LTBA)

A solution of 2,2-disubstituted-cycloalkane-1,3-dione (0.5 mmol) in THF (4 mL) was cooled at −60 °C for 1 h. In

a separate RBF was added LTBA (191 mg, 0.75 mmol) and THF (5 mL). The LTBA suspension was drawn into a glass syringe and added to the substrate dropwise over 5 min. Once the reaction was judged complete (TLC), the reaction was quenched by the addition of 1 N HCl (5 mL) then diluted with EtOAc (5 mL). After initial separation, the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic extracts were dried ($MgSO_4$) then concentrated. The resulting crude compound was examined by ^1H NMR spectroscopy then purified by flash chromatography.

5.6. Monoreduction products

5.6.1. Diastereomeric mixture of cis- and trans-(±)-2-allyl-3-hydroxy-2-methylcyclohexanone (**2a**) and (**2b**)

Purification of the crude reaction mixture by flash chromatography (8:2 hexanes/EtOAc) yielded an inseparable mixture of ketols **2a** and **2b** as a colorless oil.[21]

5.6.2. Diastereomeric mixture of cis- and trans-(±)-3-hydroxy-2-methyl-2-propylcyclohexanone (**3a**) and (**3b**)

Purification of the crude reaction mixture by flash chromatography (9:1 EtOAc/hexanes) yielded an inseparable mixture of ketols **3a** and **3b** as a clear, yellow oil.[21]

5.6.3. Diastereomeric mixture of cis- and trans-(±)-2-benzyl-3-hydroxy-2-methylcyclohexanone (**4a**) and (**4b**)

Purification of the reaction mixture by flash chromatography (9:1 hexanes/EtOAc) yielded ketols **4a** and **4b** as a colorless oil. **4a**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.26–7.15 (m, 5H), 3.82 (m, 1H, trans), 3.75 (m, 1H, cis), 3.11 (d, 1H, J=13.5 Hz, cis), 2.96 (d, 1H, J=13.5 Hz, cis), 2.87 (d, 1H, J=13.5 Hz, trans), 2.56–2.53 (m, 2H, cis), 2.16–2.08 (m, 1H, cis), 2.05–1.99 (m, 1H), 1.92 (br s, 1H), 1.89–1.82 (m, 1H, cis), 1.79–1.72 (m, 1H, cis), 1.12 (s, 3H, trans), 1.07 (s, 3H, cis); ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.9 (cis), 213.7 (trans), 137.7 (trans), 137.5 (cis), 130.5 (cis), 130.4 (trans), 128.2 (trans), 128.0 (cis), 126.4 (trans), 126.2 (cis), 75.6 (cis), 74.1 (trans), 55.7 (trans), 54.4 (cis), 41.0 (trans), 37.7 (cis), 37.2 (cis), 28.7 (trans), 28.5 (cis), 20.7 (cis), 20.3 (cis), 20.1 (trans), 18.2 (trans); IR (thin film, cm^{-1}): 3449, 3084, 3061, 3028, 2941, 2874, 1698, 1603, 1495, 1453, 758, 705; HRMS (EI): calcd for $C_{14}H_{18}O_2$ $[M]^+$ 218.1307, found 218.1308.

5.6.4. cis-(±)-3-Hydroxy-2-methyl-2-propargyl-cyclohexanone (**5a**)

The compound was purified by flash chromatography (85:15 hexanes/EtOAc) affording a clear, colorless oil.[21]

5.6.5. trans-(±)-3-Hydroxy-2-methyl-2-propargyl-cyclohexanone (**5b**)

The compound was purified by flash chromatography (85:15 hexanes/EtOAc) affording a clear, colorless oil.[21]

5.6.6. Diastereomeric mixture of cis- and trans-(±)-2-cyanoethyl-3-hydroxy-2-methylcyclopentanone (**6a**) and (**6b**)

Purification of the crude reaction mixture by flash chromatography (9:1 DCM/EtOAc) yielded an inseparable mixture of ketols **6a** and **6b** as a clear, colorless oil.[21]

5.6.7. Diastereomeric mixture of cis- and trans-(±)-2-allyl-3-hydroxy-2-methylcyclopentanone (**8a**) and (**8b**)

Purification of the crude reaction mixture by flash chromatography (8:2 hexanes/EtOAc) yielded an inseparable mixture of ketols **8a** and **8b** as a clear, colorless oil.[21]

5.6.8. cis-(±)-3-Hydroxy-2-methyl-2-propylcyclopentanone (**9a**)

The compound was purified by flash chromatography (9:1 hexanes/EtOAc) affording a clear, slightly yellow oil.[21]

5.6.9. Diastereomeric mixture of cis- and trans-(±)-2-benzyl-3-hydroxy-2-methylcyclopentanone (**10a**) and (**10b**)

Purification of the crude reaction mixture by flash chromatography (8:2 hexanes/EtOAc) yielded an inseparable mixture of ketols **10a** and **10b** as a cloudy, colorless oil. **10a**: ^1H NMR (500 MHz, $CDCl_3$): δ 7.28–7.13 (m, 5H), 4.20 (t, 1H, J=7.5 Hz, trans), 4.05 (t, 1H, J=3.5 Hz, cis), 3.06 (d, 1H, J=14.0 Hz, cis), 2.89 (d, 1H, J=13.5 Hz, trans), 2.72 (d, 1H, J=14.0 Hz, cis), 2.70 (d, 1H, J=13.5 Hz, trans), 2.55–2.47 (m, 1H, cis), 2.40–2.33 (m, 1H, cis), 2.21–2.14 (m, 1H, cis), 2.04 (br s, 1H, cis), 1.92–1.86 (m, 1H, cis), 1.04 (s, 3H, trans), 0.87 (s, 3H, cis); ^{13}C NMR (125 MHz, $CDCl_3$): δ 220.6 (cis), 220.1 (trans), 137.9 (cis), 137.3 (trans), 130.4 (cis), 130.0 (trans), 128.4 (trans), 128.1 (cis), 126.7 (trans), 126.2 (cis), 76.3 (cis), 74.1 (trans), 54.8 (cis), 54.1 (trans), 41.1 (trans), 35.7 (cis), 35.3 (trans), 33.7 (cis), 28.2 (cis), 27.3 (trans), 19.6 (cis), 16.1 (trans); IR (thin film, cm^{-1}): 3433, 3086, 3062, 3028, 2967, 2928, 2875, 1728, 1647, 1496, 1454, 1159, 1143, 1073, 1034, 736, 704; HRMS (EI): calcd for $C_{13}H_{16}O_2$ $[M]^+$ 204.1150, found 204.1150.

5.6.10. cis-(±)-3-Hydroxy-2-methyl-2-propargyl-cyclopentanone (**11a**)

The compound was purified by flash chromatography (8:2 hexanes/EtOAc) affording a clear, colorless oil.[21]

5.6.11. trans-(±)-3-Hydroxy-2-methyl-2-propargyl-cyclopentanone (**11b**)

The compound was purified by flash chromatography (8:2 hexanes/EtOAc) affording a clear, colorless oil.[21]

5.6.12. cis-(±)-2-Cyanoethyl-3-hydroxy-2-methyl-cyclopentanone (**12a**)

The compound was purified by flash chromatography (9:1 DCM/EtOAc) affording a clear, colorless oil.[21]

5.6.13. trans-(±)-2-Cyanoethyl-3-hydroxy-2-methyl-cyclopentanone (**12b**)

The compound was purified by flash chromatography (9:1 DCM/EtOAc) affording a clear, colorless oil.[21]

*5.6.14. cis-(±)-3-Hydroxy-2-methyl-2-phenyl-cyclopentanone (**15a**)*

The compound was purified by flash chromatography (8:2 hexanes/EtOAc) affording a cloudy, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39–7.28 (m, 5H), 4.22 (m, 1H), 2.72–2.64 (m, 1H), 2.54–2.48 (m, 1H), 2.31–2.23 (m, 1H), 2.10–2.07 (m, 1H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.0, 138.2, 128.8, 128.0, 127.4, 78.9, 59.0, 35.4, 26.9, 22.0; IR (thin film, cm^{-1}): 3442, 2972, 2926, 1735, 1447, 1157, 1055, 734, 701; HRMS (EI): calcd for $C_{12}H_{14}O_2$ $[M]^+$ 190.0994, found 190.1001.

*5.6.15. cis-(±)-3-Hydroxy-2-methyl-2-(nitroethyl)-cyclopentanone (**16a**)*

The compound was purified by flash chromatography (92:8 DCM/EtOAc) affording a clear, light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.54–4.50 (m, 2H), 4.13 (m, 1H), 2.55–2.49 (m, 1H), 2.32–2.08 (m, 5H), 1.92–1.85 (m, 1H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 218.3, 75.9, 71.4, 51.1, 34.8, 32.1, 27.7, 14.2; IR (thin film, cm^{-1}): 3432, 2971, 2926, 1733, 1638, 1552; HRMS (EI): calcd for $C_8H_{13}NO_4$ $[M-OH]^+$ 170.0817, found 170.0818.

*5.6.16. trans-(±)-3-Hydroxy-2-methyl-2-(nitroethyl)-cyclopentanone (**16b**)*

The compound was purified by flash chromatography (92:8 DCM/EtOAc) affording a clear, light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.61–4.50 (m, 2H), 4.13 (t, 1H, J=3.5 Hz), 2.53–2.46 (m, 1H), 2.38–2.21 (m, 4H), 2.00–1.94 (m, 1H), 1.84 (br s, 1H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.0, 77.1, 72.1, 51.7, 33.4, 28.4, 28.2, 19.3; IR (thin film, cm^{-1}): 3432, 2971, 2926, 1733, 1638, 1552; HRMS: calcd for $C_8H_{13}NO_4$ $[M]^+$ 187.0845, found 187.0841.

*5.6.17. cis-(±)-6-Methyl-2-oxabicyclo[4.3.0]nonane-3,7-dione (**17a**)*

The compound was purified by flash chromatography (1:1 EtOAc/hexanes) affording a clear, colorless oil.[21]

*5.6.18. trans-(±)-Methyl 3-(5-hydroxy-1-methyl-2-oxocyclopentyl)propanoate (**17b**)*

The compound was purified by flash chromatography (1:1 EtOAc/hexanes) affording a clear, colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.11–4.07 (m, 1H), 3.68 (s, 3H), 2.51–2.45 (m, 1H), 2.43–2.16 (m, 4H), 2.06 (d, 1H, J=4.0 Hz), 1.92–1.74 (m, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 219.3, 174.5, 75.6, 52.5, 51.9, 34.8, 29.3, 28.8, 27.2, 14.7; IR (thin film, cm^{-1}): 3421, 2957, 2924, 2853, 2360, 2341, 1734, 1073; HRMS (EI): calcd for $C_{10}H_{16}O_4$ $[M]^+$ 200.1049, found 200.1046.

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