Article Type: Full Paper

Regioselective Dialkylations of *N*-(*tert*-Butyl)iminocyclopentane via Deprotonating One-Pot Procedures

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Key words: Azaallyllithium; *N*-lithioenamines; sp^2-nitrogen inversion; spiroacetals; spiro[2.4]heptan-4-ones

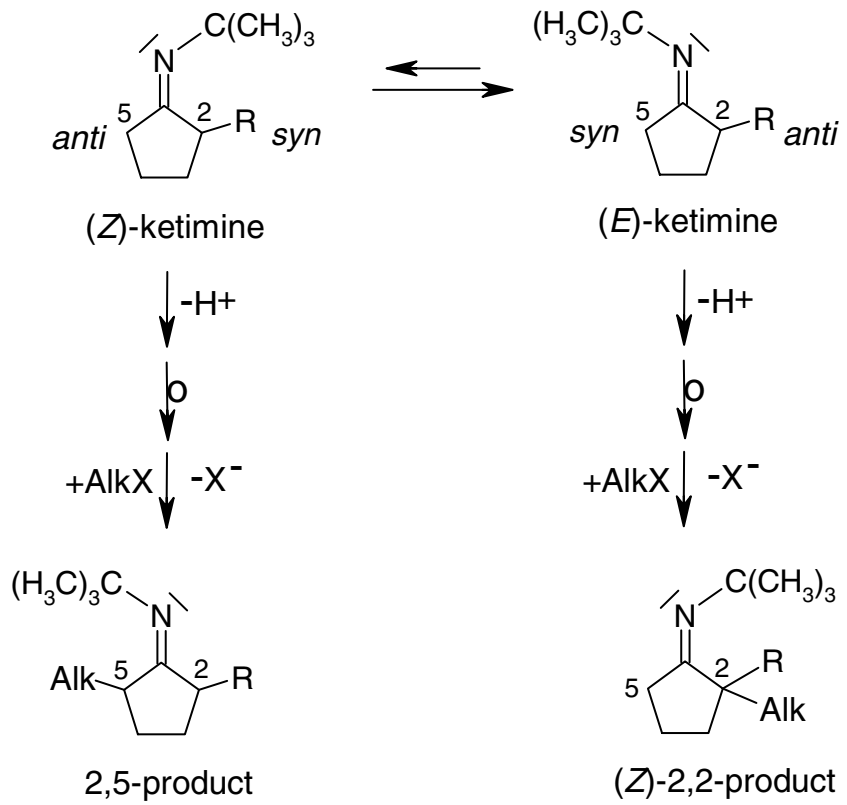
Abstract. The title compound (**1**) was chosen as a model for the α/α´-regioselectivity of deprotonation and subsequent alkylation adjacent to the C=N double bond. With the bulky base lithium *N*,*N*-diisopropylamide (LDA) as a catalyst, the one-pot deprotonation steps can be performed through titration with methyllithium, using gas-volumetric observation of the liberated methane. In the first step with ensuing methylation by iodomethane, the primary product is born at –40 °C in its metastable *Z* configuration (kinetic control) and may be either isolated or converted in situ at 30 °C into its thermodynamically favored (*E*)-isomer via *cis* to *trans* stereoinversion at the nitrogen atom. Being slow enough on the laboratory time scale, this stereoinversion process can serve to control the regioselectivity of the second deprotonation/alkylation sequence as follows. The α,α´-products are formed from the intermediate (*Z*)-imine, whereas α,α-products result from the intermediate (*E*)-imine; in either case, *syn* deprotonation (*cis* to tBu at nitrogen) by LDA is apparently disfavored by the tBu group, so that *anti* deprotonation becomes obligatory. If a third one-pot deprotonation

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/hlca.201800037

step is too slow with LDA, it may be performed with the stronger base *n*-butyllithium/HMPA which, however, reacts regio-unselectively. Regioselective one-pot, LDA-catalyzed deprotonation with alkylation by oxiranes (alone, or alternatingly with iodomethane) opens a short access to spiro[2.4]heptan-4-ones.

1. Introduction

Regioselectively controlled deprotonation of ketimines ($R^3N=CR^1R^2$) was developed through meticulous mechanistic elucidations.[1 - 3] It may serve as a tool for the introduction of substituents whose accurate (α- or α') positioning would be difficult with the "parent" ketones $O=CR^1R^2$ (especially with monosubstituted cyclopentanones). Scheme 1 displays our presently employed ketimine model system and the products of its anticipated regioselective trapping by an alkylating agent AlkX: It illustrates how the ketimine configuration (*Z* or *E*) should determine the regioselectivity of removing a proton from the *anti* position, namely, *trans* to the *tert*-butyl ("tBu") group at nitrogen. Such deprotonations are accompanied by a rapid rearrangement which directs the entailing alkylation to give primary products with a *syn* relationship of the entering agent ("Alk") and the N–tBu group. This established[1] mechanism explained the surprising formation of a (*Z*)-2,2-product (Scheme 1) from an (*E*)-ketimine through that most advantageous rearrangement of an intermediate 1-azaallyllithium compound (not shown here). The same mechanistic principles apply to the monoalkylation of the title compound **1** with the initial formation of the (*Z*)-ketimine (with R = alkyl in Scheme 1) and its second alkylation that generates the 2,5-product.



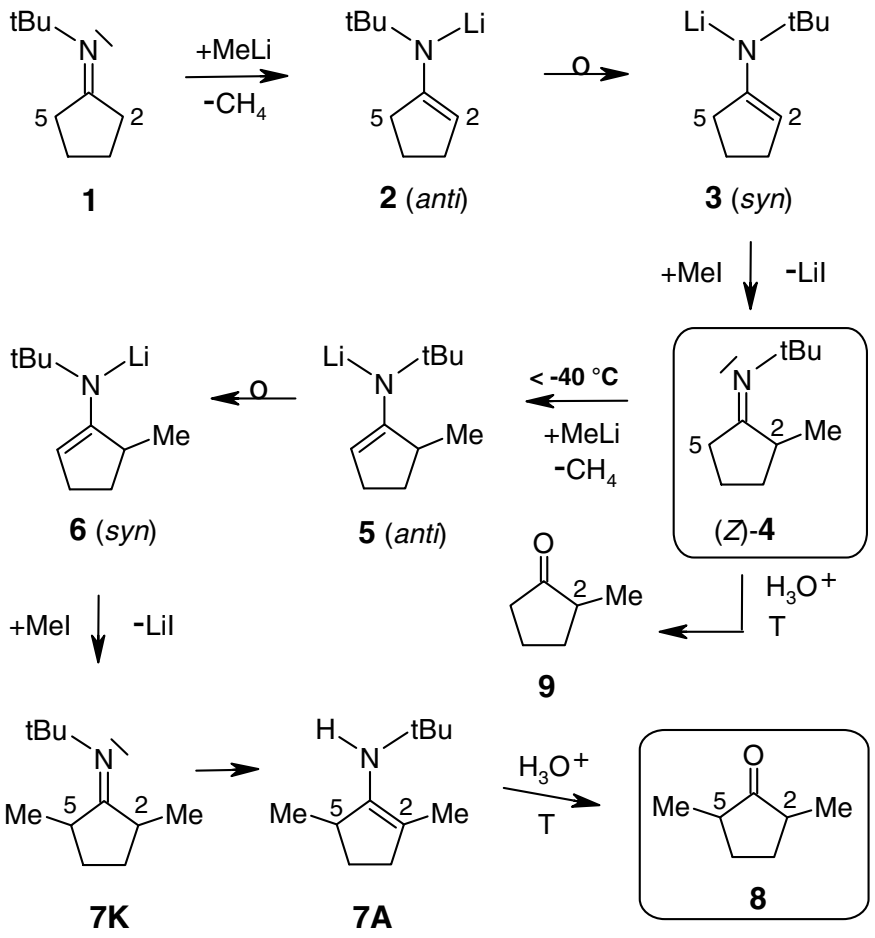
Scheme 1. *Anti* deprotonation and alkylation of the *Z*,*E* ketimine diastereomers.

The possibility to use the =N–tBu orientation as a control instrument depends on the direction and velocity of the *Z*,*E* re-orientations. These *Z*,*E* stereoinversion processes were too fast for controlling purposes in the case of an *N*-aryl model[4] that produced comparable amounts of the 2,5- and 2,2-products.[5] The earlier studied *N*-alkylimine model systems were reported[1,2] to depend on further factors; but they suggested to us that an N–tBu moiety might favor the *anti* over the alternative *syn* deprotonation sufficiently to control the regioselectivity. Such an important simplification in combination with the suitably slow *Z*,*E* interconversion convinced us to investigate the =N–tBu model depicted in Scheme 1.

2. Results and discussion

2.1. Preparation and dimethylation of the ketimine 1.

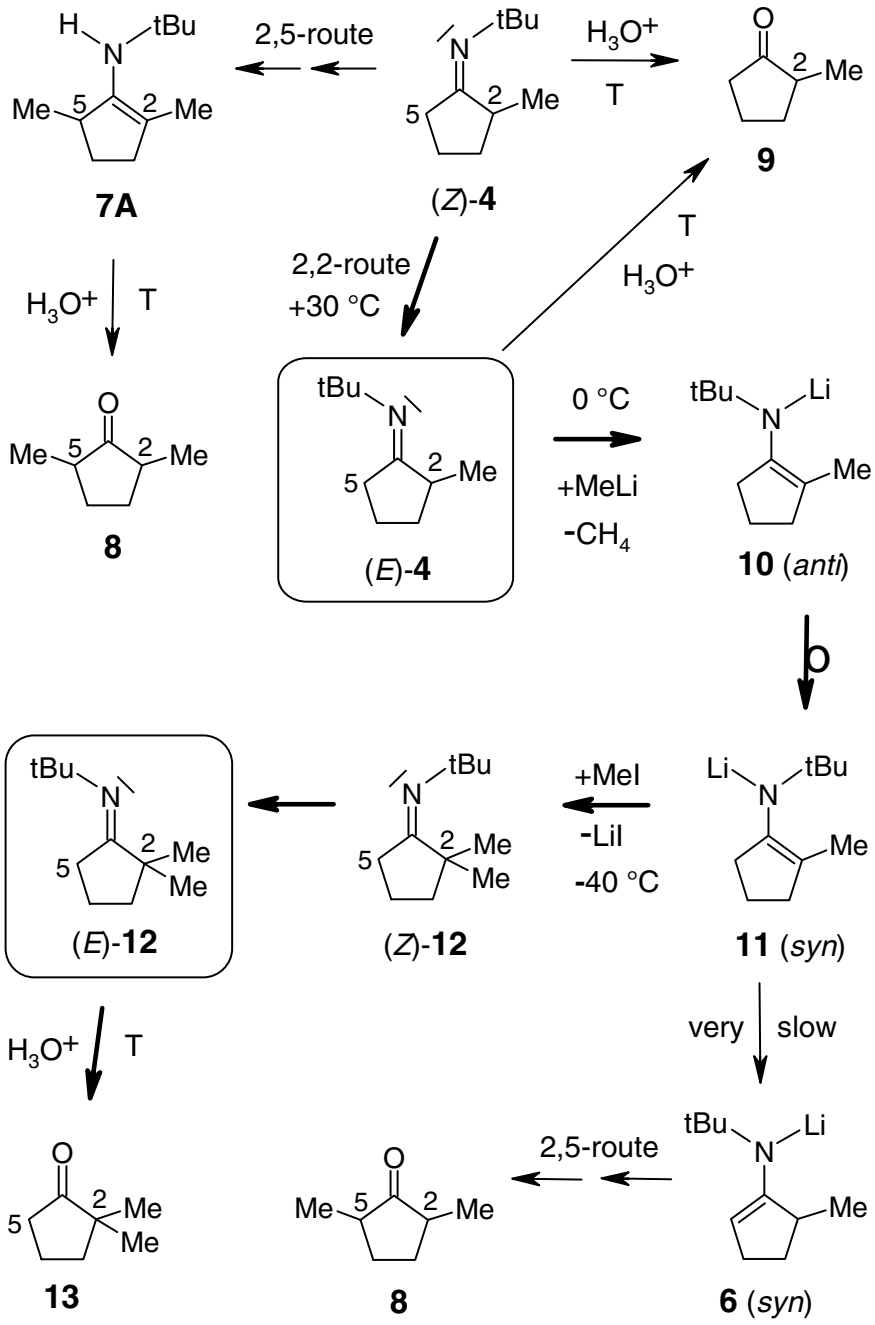
The known[6] title compound *N*-(cyclopentylidene)-*tert*-butylamine (**1**) was prepared from cyclopentanone and *tert*-butylamine (3 equiv) with $TiCl_4$ (0.52 equiv),[7] using some modifications that increased the yield of **1** slightly. Its NMR spectra were taken in CCl_4 or [D_6]benzene as the solvent because its solutions in commercial $CDCl_3$ deteriorated quickly. The bulky base lithium *N*,*N*-diisopropylamide (LDA) had usually been employed to abstract a proton from the azaallyl-type (α) position of ketimins (such as the 2-position of **1** in Scheme 2). With **1** and some of its intermediates as the CH acids, we found it convenient to generate LDA in situ from *N*,*N*-diisopropylamine (0.14 equiv) and methyllithium as a base whose consumption could be measured simply by means of the gas volume of the emanating methane. According to the well-stablished[1,2] deprotonation mechanism, the azaallyllithium (an *N*-lithioenamine) intermediate **2** should be generated through proton transfer from the *anti* position ($H_2C(2)$ in **1**) to LDA; the by-product *N*,*N*-diisopropylamine will then be reconverted to LDA by additional H_3CLi. An accompanying fast rearrangement of **2** should form the more stable[3,8] *syn* azaallyllithium **3**. Thus, we performed this LDA-catalyzed deprotonation of **1** in THF at –40 °C (General Procedure GP1) through titration with H_3CLi in Et_2O; subsequent trapping of **3** at –70 °C with iodomethane (MeI, 1 equiv) generated the metastable ketimine (*Z*)-**4**. This key compound controls the regioselectivity: Its *anti* position ($H_2C(5)$) remains available for a second deprotonation as long as (*Z*)-**4** does not isomerize into the more stable (*E*)-**4**. Therefore, the obtained solution of (*Z*)-**4** and LDA was allowed to warm up to –40 °C only (GP2a), at which temperature it was promptly titrated with a second portion of H_3CLi (up to 1.15 equiv). Again, the immediately generated azaallyllithium **5** (*anti*) rearranged quickly to **6** (*syn*). When the evolution of CH_4 ceased after 12 min, **6** was trapped with MeI (1.2 equiv) at –40 °C to give the ketimine **7K**. Like all other ketimines obtained in this work, **7K** could be dissolved in cold aqueous HCl (2 M) without being hydrolyzed, so that it could easily be separated from all nonbasic contaminants. Upon alkalization (GP2c) of the HCl solution, **7K** returned as the tautomeric enamine **7A** without any other isomeric form. Since small amounts of other basic contaminants were still present, this material was subjected to acid-catalyzed, de-aminating hydrolysis by boiling aqueous H_2SO_4 (2 N, GP3), whereby it furnished a distilled mixture (35% yield) of 2,5-dimethyl- (**8**) and 2-methylcyclopentanone (**9**) in a molar ratio of 95:5. The presence of **9** disclosed that the conditions of the second methylation were insufficient to consume **4** completely; however, this dimethylation of **1** was so highly regioselective that no 2,2-product could be detected.



Scheme 2. Intermediates and products of LDA-mediated methylation on the 2,5-route; Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

The alternative "2,2-route" was opened when we warmed the THF/Et_2O solution of the metastable 2-methyl product (*Z*)-**4** (Scheme 3) quickly from –40 °C to +30 °C and stirred it for 2 hours (GP2b). During this period of time,[9] (*Z*)-**4** was transformed into the preponderant diastereomer (*E*)-**4**. Although (*E*)-**4** offered a normally less reactive *tert*-CH group at its *anti* position C(2), the subsequent second titration with H_3CLi led to a comfortably fast CH_4 evolution with formation of the azaallyllithium **10** (*anti*) that rearranged quickly to the thermodynamically favored[3,8] isomer **11** (*syn*). Trapping of **11** with MeI (1.2 equiv) at –40 °C and subsequent stirring at room temperature (rt) for 90 min generated the 2,2-dimethyl ketimine (*E*)-**12** via its less stable diastereomer (*Z*)-**12**. After separation from the nonbasic contaminants through extraction into cold aqueous HCl (2 M, GP2c) and subsequent alkalization, the obtained sample of (*E*)-**12** contained minor basic side-products, so that the presence of an enamine or of a small 2,5-dimethyl fraction

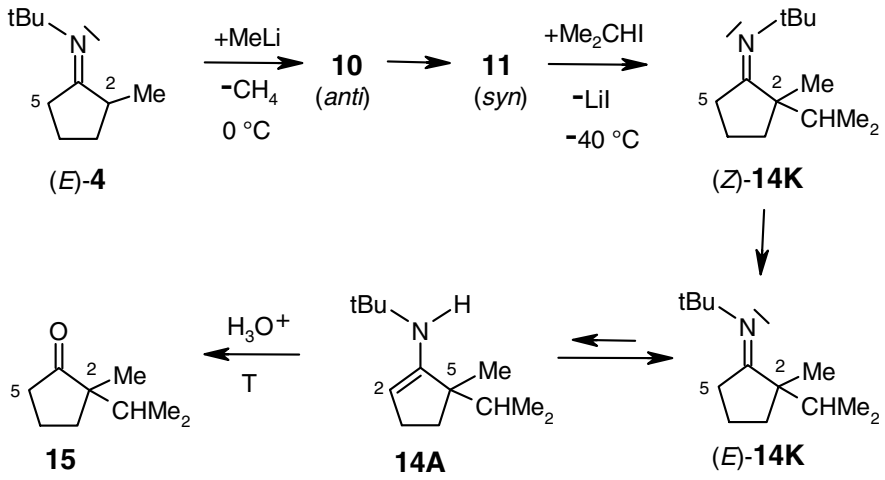
could not yet be ascertained. In order to arrive at a reliable analysis, the basic fraction was subjected to the acid-catalyzed, de-aminating hydrolysis (GP3), which afforded a distilled mixture (45% yield) of 2,2-dimethyl- (**13**), 2,5-dimethyl- (**8**), and 2-methylcyclopentanone (**9**) in the molar ratio of 92:3:3. Hence, the formation of **9** disclosed that the conditions of the second deprotonation were again insufficient to consume the monomethyl ketimine **4** completely. The **13**/**8** = 92:3 regioselectivity seemed to point into the direction of the 87:13 ratio that may be expected[10] for the (*E*)-**4**/(*Z*)-**4** equilibrium (upper part of Scheme 3). Alternatively, leakage from the 2,2- to the 2,5-route might have occurred by a slow protonation/deprotonation process (bottom part of Scheme 3) that transformed **11** (*syn*) into **6** (*syn*) and may be catalyzed[11] by traces of a CH-acidic ketimine. We actually discovered such a leakage under considerably harsher conditions : A slow conversion of **11** into **6** was detected after 3 hours in THF at 60 °C (but not yet after 64 hours at rt) through methylation and hydrolysis as above, which furnished the 2,2-/2,5-products (ketones **13** and **8**) as a 53:37 mixture instead of the above 92:3 ratio. The converse protonation/deprotonation process under the same conditions with heating of **6** in the initial absence of **11** suggested that the equilibrium ratio of **11**/**6** was ca. 6:87. These observations established an **11** $\rightarrow$ **6** leakage that appeared to be significantly slower than the corresponding leakage process described[1] in the literature. As a consequence, the **11** $\rightarrow$ **6** leakage can be excluded under the milder conditions of our GP2b, which leaves the hypothesis of an LDA-repellent N–tBu group that impeded *syn* deprotonation by LDA but admitted the observed *anti* deprotonations of both (*Z*)-**4** and the (*E*,*Z*)-**4** equilibrium mixture.



Scheme 3. Intermediates and products of LDA-mediated methylation on the 2,2-route (bold arrows); Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

The second C(2) alkylation was regiospecific also with 2-iodopropane as one of the sterically handicapped electrophiles: With the "LDA-repellent N–tBu" group adjusted for the 2,2-route, (*E*)-**4** generated a 89:11 mixture of the ketimine **14K** and its enamine **14A** (75% yield of all basic products).

The presence of other basic contaminants thwarted our attempts to establish the absence of a 2,5-isomer of **14**; however, the acid-catalyzed, de-aminating hydrolysis (GP3) afforded a 55% yield of the known[12,13] 2-isopropyl-2-methylcyclopentanone (**15**) without the 2,5-isomer. This confirmed the 2,2-regiospecific process as far as the missing 2,5-ketimine would have been expected to be hydrolyzed faster than **14K**.

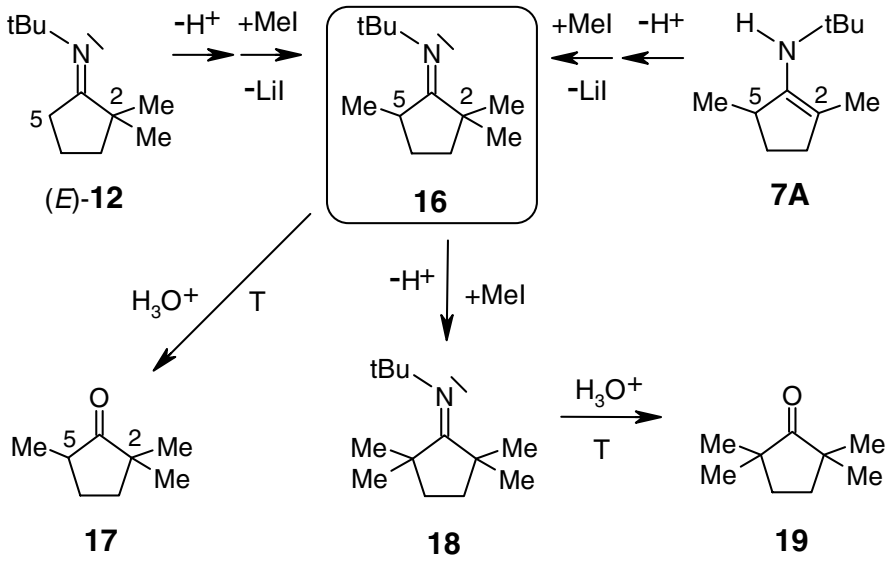


Scheme 4. LDA-mediated, regiospecific isopropylation of (*E*)-**4**; Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

2.2. Convergent trimethylation.

As a short outlook beyond *anti* regioselectivity, the formation of tri- and tetramethylated ketimines should be possible from both 2,5- (**7A**) and 2,2-dimethyl (**12**) precursors: (*E*)-**12** (Scheme 5) must be deprotonated at C(5) either by the slower *syn* attack or via regeneration of the less favored equilibrium component (*Z*)-**12** and an ensuing *anti* deprotonation; in either case, (*E*)-**12** is expected to generate the 2,2,5-trimethyl ketimine **16** rather slowly. Actually, (*E*)-**12** was prepared through the GP2b process and treated in situ with additional *N*,*N*-diisopropylamine (0.60 equiv) and H_3CLi (1.2 equiv) at 42 °C for 2 hours, then quenched with MeI (1.2 equiv) at 0 °C. One repetition of the latter deprotonation/methylation sequence (in the vain hope for tetramethylation) and subsequent work-up (GP2c) afforded a basic product fraction (91% yield) that contained **16** and unconsumed (*E*)-**12** in a 48:52 ratio. This evidence for such a slow deprotonation of (*E*)-**12** by LDA had been obtained through acid-catalyzed, de-aminating hydrolysis (GP3, 1 hour) which left 53% of ketimine **16** intact; the hydrolyzed and distilled portion (27% yield) contained a 77:23 mixture of 2,2-

dimethyl (**13**, from residual **12**) and 2,2,5-trimethylcyclopentanone (**17**). Thus, both the deprotonation of (*E*)-**12** and the hydrolysis of **16** were slow processes.



Scheme 5. 2,2,5-Trimethyl- (**17**) and (almost no) 2,2,5,5-tetramethylcyclopentanone (**19**) were formed from enamine **7A** or ketimine **12**; Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

Under the above conditions of a twofold LDA-mediated deprotonation/methylation sequence, the 2,5-dimethyl enamine **7A** (from GP2a) furnished a basic fraction (65% yield) that contained mainly the 2,2,5-trimethyl ketimine **16**. Acid-catalyzed, de-aminating hydrolysis (GP3, 1 hour) left again 47% of **16** intact and afforded a distilled 93:7 mixture (9 % yield) of 2,2,5-trimethyl- (**17**) and 2,2-dimethylcylopentanone (**13**, from residual **12**), the latter as a reminiscence of the monomethyl ketimine **4** that had survived the GP2a treatment (Scheme 3) and generated now the sluggish 2,2-ketimine **12** at 42 °C. Tetramethylated compounds (**18** or **19**) were not observed in these runs with LDA and MeI.

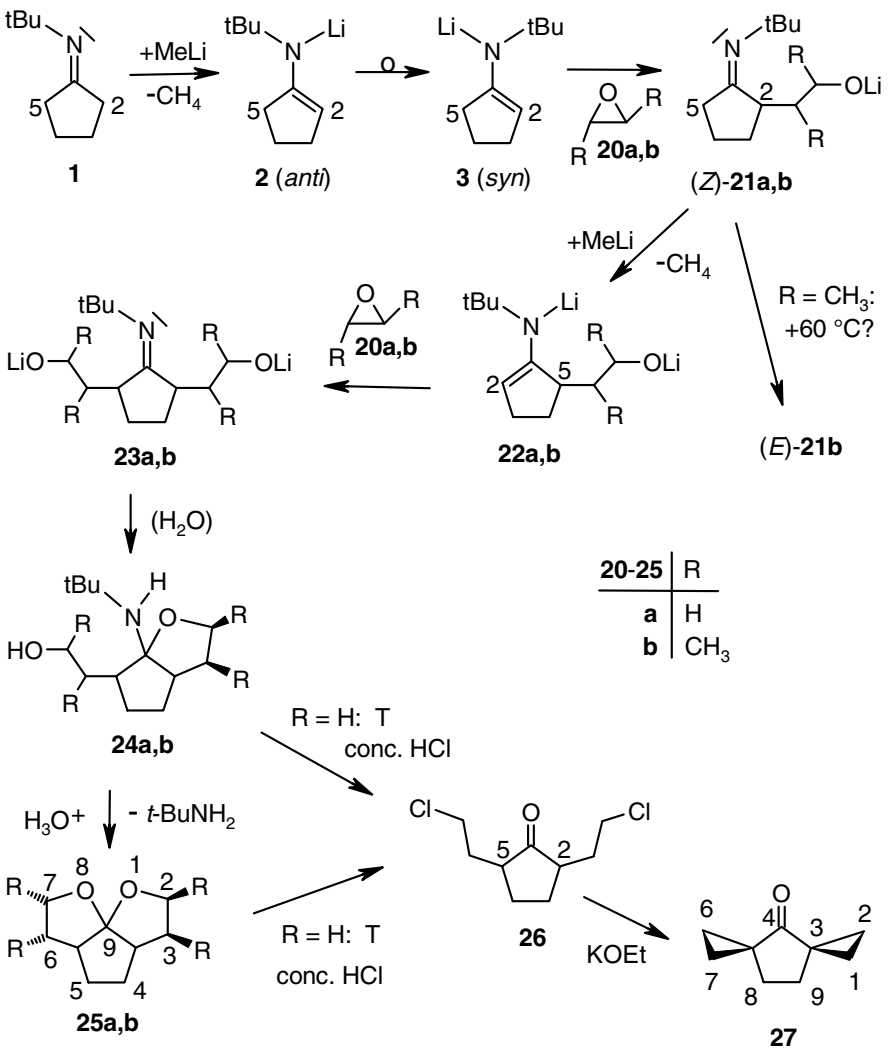
For a more efficient third deprotonation, we used the stronger base *n*-butyllithium (*n*-BuLi) in combination with hexamethylphosphoramide (HMPA) which had been reported[14] to prefer *syn* deprotonation. The formerly sluggish 2,2-dimethyl ketimine (*E*)-**12**, prepared again in THF/Et_2O with LDA/H_3CLi (GP2b), was now consumed completely by the twofold in situ treatment with the sequence of deprotonation (2 hours at rt) and methylation. The basic fraction (96% yield) from GP2c carried the 2,2,5-trimethyl- (**16**) and 2,2,5,5-tetramethyl ketimine (**18**) in a 99:1 ratio as determined

through acid-catalyzed, de-aminating hydrolysis (GP3, 1 hour) that afforded a mixture (8% yield) of 2,2,5-trimethyl- (**17**) and 2,2,5,5-tetramethylcyclopentanone (**19**) beside residual **16** (43%). Under the same conditions, the enamine **7A** was subjected to the twofold in situ treatment with *n*-BuLi (1.2 equiv) and HMPA (1 equiv) and MeI (1.2 equiv). The resultant basic fraction (yield 99%) was hydrolyzed (GP3, 1 hour, yield 11%) to give **17** and **19** (99:1) again together with unconsumed **16** (52%). In short, trimethylation of ketimine **1** was conveniently performed using *n*-BuLi/HMPA for the third deprotonation after the GP2a or GP2b process, whereas tetramethylation was almost impossible because of the bulky N-tBu group.

The non-optimized one-pot procedures described in this Section exemplified how the ketimine **1** can successfully be mono- or trialkylated or regioselectively dialkylated.

2.3. Alkylation by oxiranes as the electrophiles

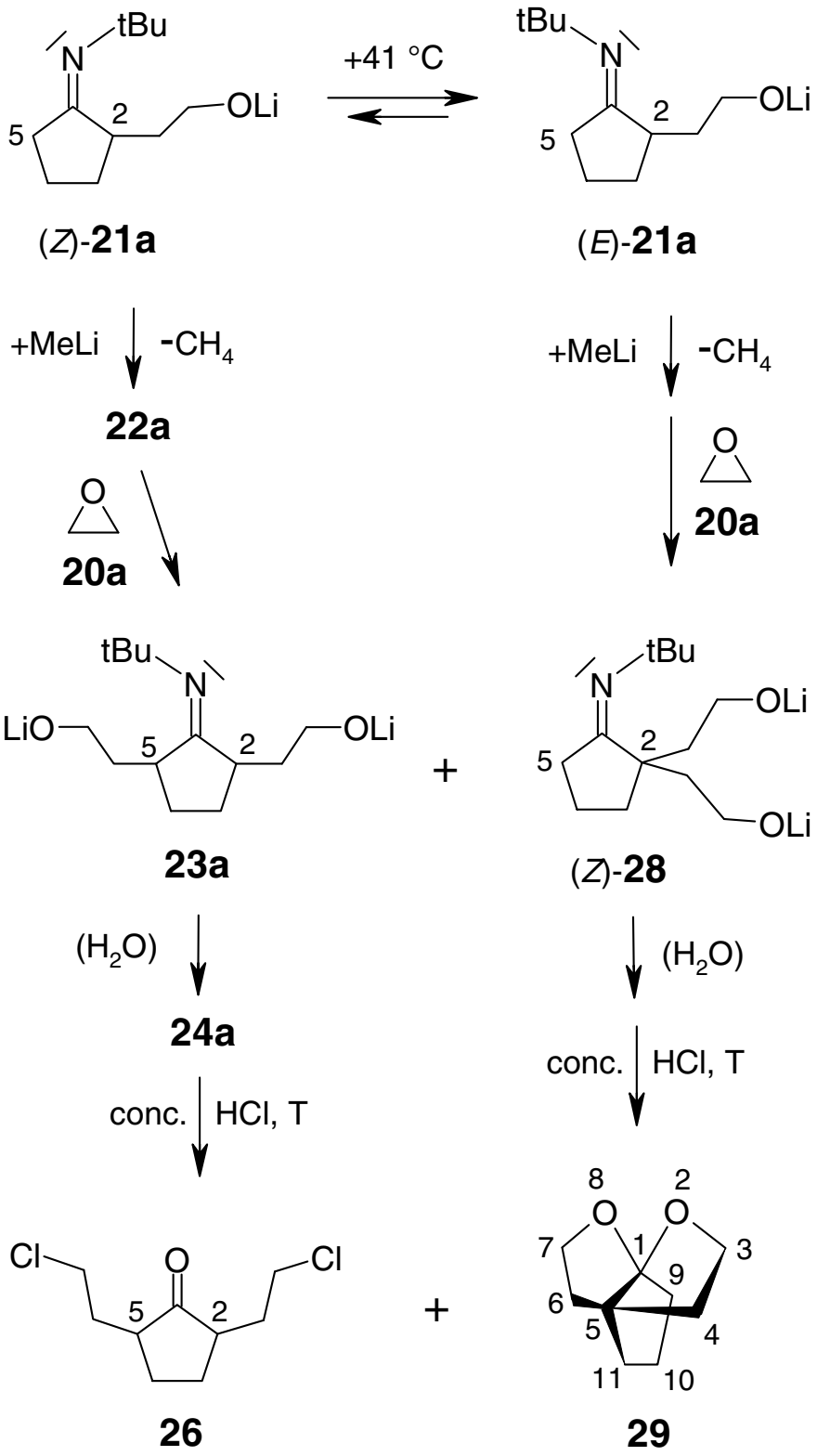
Selection of the 2,5-route can also be achieved with ethylene oxide (**20a** in Scheme 6) under the conditions of obligatory *anti* deprotonation by LDA: In the spirit of Scheme 2, the first alkylation (GP1) of ketimine **1** is expected to generate only (*Z*)-**21a**. At sufficiently low temperatures (GP2a) that do not yet admit a *Z* to *E* stereoinversion, (*Z*)-**21a** will be deprotonated at its *anti* position (C(5)) to generate the azaallylithium **22a** that undergoes the second alkylation to give the primary 2,5-dialkylated product **23a**. As ethylene oxide (**20a**) is unreactive toward both LDA and H_3CLi under the reaction conditions, the ketimine **1** can (but must not) be deprotonated in the presence of **20a** (3.0 equiv) by LDA (0.14 equiv) with H_3CLi (2.1 equiv). This is, of course, the most simple way to deprotonate (*Z*)-**21a** as soon as it is born. Aqueous work-up disclosed that the ketimine product expected from **23a** had been cyclized with formation of the N,O-acetal[15] **24a**: The IR spectrum of crystalline **24a** displayed neither C=O nor C=N vibrations, and the ^{13}C (no C=O, no C=N functions) and ^{1}H NMR spectra revealed that **24a** was a pair of diastereomers (ca. 1:1) whose resonances could not be distinguished and assigned. The 2,5-constitution of **24a** was established through acid-catalyzed, de-aminating hydrolysis (GP3): The resultant, bridged spiro[4.4]acetal[16] **25a** can be formed from both diastereomers of **24a** due to the known[17] configutational lability of spiroacetals in strongly acidic solutions. The 2,5-stereoselective formation of **24a** was further established with the following derivatives. Both **24a** and **25a** were ring-opened in boiling conc. HCl (GP4) that furnished the known[18] 2,5-bis(2´-chloroethyl)cyclopentanone (**26**) as a 4:1 *trans*/*cis* mixture. The KOEt-mediated HCl elimination (GP5) from **26** completed the present, reasonably short approach[19,20] to the known[21] dispiro ketone **27**.



Scheme 6. LDA-mediated 2,5-dialkylation of **1** with two oxiranes (**20a**,**b**); Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

The above-mentioned unreactivity of ethylene oxide (**20a**) against LDA and H_3CLi offered an opportunity to study a dialkylation reaction of **1** under conditions of (*Z*)-**21a** → (*E*)-**21a** stereoinversion (Scheme 7). The question was if the primary product (*Z*)-**21a** might undergo in-situ deprotonation (the 2,5-route) less readily than stereoinversionwith subsequent generation of the 2,2-product (*Z*)-**28**. Using the same reactant ratios as above, H_3CLi (2.1 equiv) was added dropwise at 41 °C (rather than at –40 °C) to the rapidly stirred THF solution of ethylene oxide (**20a**, 3 equiv) and *N*,*N*-diisopropylamine (0.14 equiv). After work-up (GP2c), the basic fraction was treated with

boiling conc. HCl (GP4) and furnished a mixture (ca. 1:1) of the 2,5-product **26** (from **24a** in Schemes 6 and 7) and the 2,2-acetal **29** (from **28**). In contrast to the bridged spiro[4.4]acetal **25a**, the 2,2-product dioxapropellane[3.3.3] **29** (a tricyclo[3.3.3.$0^{1,5}$]undecane) was obviously stable against hot conc. HCl. The resultant **26**/**29** mixture established that (*Z*)- and (*E*)-**21a** had performed *anti* deprotonations with subsequent alkylations by **20a** to generate **24a** and **28** in parallel. The results convinced us to confine our further attempts to the 2,5-route.



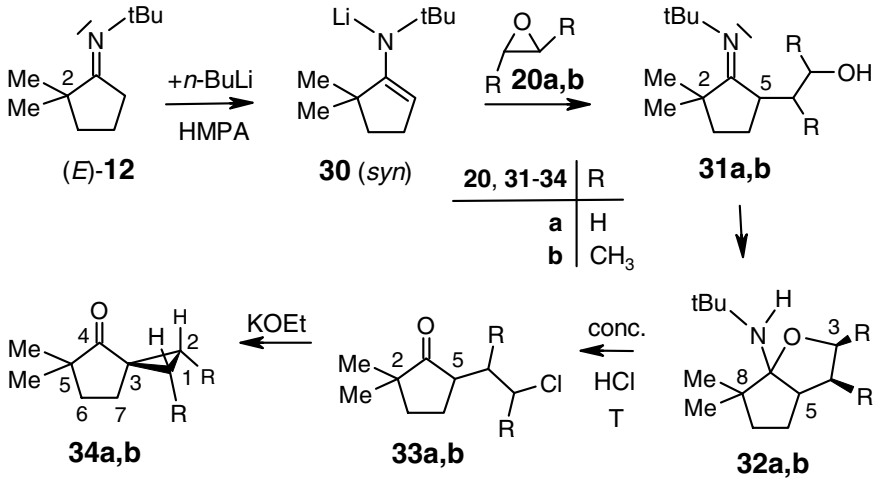
Scheme 7. LDA-mediated, parallel 2,5- and 2,2-dialkylation by ethylene oxide (**20a**) at 41 °C; Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

Returning to Scheme 6, we report that racemic *trans*-2,3-dimethyloxirane (**20b**) is significantly less reactive than **20a** yet (under suitably changed conditions) able to run through the 2,5-dialkylation cascade of ketimine **1** downwards to the bridged spiro[4.4]acetal **25b**. The initial deprotonation/alkylation sequence of **1** with LDA/H_3CLi and **20b** afforded (*Z*)-**21b** smoothly; but this alkoxide could not be forced in situ to evolve CH_4 on treatment with LDA/H_3CLi at temperatures up to 60 °C, presumably because (*Z*)-**21b** had already isomerized to (*E*)-**21b** with an overcrowded *anti* position (C(2)). Therefore, we started the one-pot procedure from **1** in THF with HMPA/H_3CLi (*syn* deprotonator)[14] in the absence of LDA and observed that CH_4 (1 equiv) was liberated already at –42 °C. In order to ascertain a complete first alkylation, the oxirane **20b** was added in excess (3.1 equiv). As a consequence, the subsequent second titration with H_3CLi at 0 °C evolved CH_4 at first quickly through deprotonation[22] of unconsumed **20b** (2 equiv) by H_3CLi, followed by the desired deprotonation of **21b** (1 equiv). The generated azaallyllithium **22b** was trapped with additional **20b** (3.1 equiv) at 56 °C, which led to *slow* fading of the yellow color in the course of 2 hours. The acidic work-up (GP2c) afforded an exuberant basic product fraction. Although the expected primary product **23b** had changed into a complex mixture of cyclized N,O-acetals (such as **24b**) whose composition could not be deduced from the NMR spectra, the predominant 2,5-dialkylation was established through an attempted choride insertion with conc. HCl (GP4) that led only to de-amination: The emerging bridged 2,5-spiroacetal **25b** (36% yield with respect to **1**) was obviously resistant to ring opening by boiling conc. HCl and remained so even during 85 hours under these GP4 conditions. This kind of a Thorpe-Ingold effect can be ascribed to the four methyl groups since the above methyl-free, bridged spiro acetal **25a** had no problem to generate its dichloro ketone **26**. The NMR spectra of **25b** were compatible with a single, C_2-symmetric diastereomer; in particular, the three-bond interproton coupling constant of ^3J = 6.6 Hz of the symmetry-equivalent 2-/3-H and 6-/7-H pairs were compatible with a *cis* relationship of these protons as expected for an S_N2-type attack of the azaallyllithiums (first **3**, then **22b**) on the *trans*-2,3-dimethyloxirane (**20b**).

2.4. Oxiranes as electrophiles combined with iodomethane

The non-enolizable, almost rigid monocyclopropyl ketone **34a** (Scheme 8) was easily accessible on the 2,2-route through the following one-pot procedure and subsequent manipulations. The ketinime (*E*)-**12** was prepared (Scheme 3) from ketinime **1** along the lines of GP2b and then deprotonated in situ to give the azaallyllithium **30**. In view of the above experience with trimethylation (Section 2.2), this *syn* deprotonation was performed with HMPA/*n*-BuLi at rt for 2

hours, whereupon ethylene oxide (**20a**) was added and the mixture stirred for 60 min in a bath of 30 °C. Acidic work-up (GP2c) furnished a basic fraction containing mainly the N,O-acetal **32a** that was formed through cyclization of the primary product **31a**. The full set of the strongest ^{13}C NMR signals could be assigned to a single, preponderant diastereomer of **32a**, while the detection of minor isomers was thwarted by the accompanying impurities. Neither IR nor the ^{13}C NMR spectra of the product mixture exhibited C=N absorptions; but de-aminating ring cleavage in boiling conc. HCl (GP4) furnished the expected γ-chloro ketone **33a** (69%) as a constitutional confirmation for **32a**. The ensuing cyclization (GP5) and distillation furnished the 5,5-dimethyl spiroketone **34a** (59%). An alternative method of preparing **34a** through methylation (74%) will be commended further below.



Scheme 8. One-pot, *n*-BuLi/HMPA-mediated, third alkylation approach toward the non-enolizable spiro[2.4]heptan-4-ones **34a**,**b**; Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

The more encumbered *trans*-2,3-dimethyloxirane (**20b**) was significantly less than **20a** suited for alkylation of the intermediate azaallyllithium **30** (Scheme 8). Under the same conditions as above, the one-pot procedure of generating (*E*)-**12** and its deprotonation by HMPA/*n*-BuLi with subsequent alkylation by **20b** (2.5 equiv, 55 °C for 2 hours) generated an unresolved mixture of basic products including unconsumed (*E*)-**12** as the major component. For a possible explanation, we propose that **20b** and the strongly basic azaallyllithium **30** may have performed the planned first S_N2 alkylation to give **31b** more slowly than a proton transfer[22] from **20b** to **30**, so that (*E*)-**12** was regenerated. After a series of further deprotonation/alkylation steps, the subsequent de-aminating ring cleavage (GP4) in boiling conc. HCl (second S_N2 step) and final cylization of **33b** (GP5, third S_N2 step) produced a crude ketone mixture that required separation by distillations and column chromatography until a small sample of almost pure **34b** was obtained. These three S_N2 steps from *trans*-**20b** to **34b** predict

a *cis* relationship between the 1-/2-CH_3 groups and also between the 1-/2-H atoms, which was established by means of the ^{1}H NMR spectrum of **34b** (Figure 1) as follows. The startling shapes of the multiplets at δ = 1.46 and 0.95 ppm (Figure 1a) were simulated as an $A_3XX'A'_3$ spectral system (Figure 1b) for the CH_3–CH–CH–CH_3 part of **34b**, using the interproton coupling constants ^3J(AX) = ^3J(A′X′) = 6.5 Hz, ^4J(AX′) = ^4J(A′X) = 0.25 Hz, ^5J(AA′) = 0 Hz, and ^3J(XX′) = 9.1 Hz. The high magnitude of the latter 1-H/2-H coupling ^3J(XX′) established the expected *cis* relationship. NOESY cross peaks disclosed that the 1-/2-CH_3 protons resided in a *cis* position to the H_2C(7) protons; hence, **34b** had been formed **20b** (*trans*) stereospecifically as a single diastereomer.[23] Its very low preparative yield exemplified a limitation of our one-pot technique. On the other hand, **34b** might perhaps be accessible from *trans*-2,3-dimethyloxirane (**20b**) and the less basic enolate of 2,2-dimethylcyclopentanone (**13**).

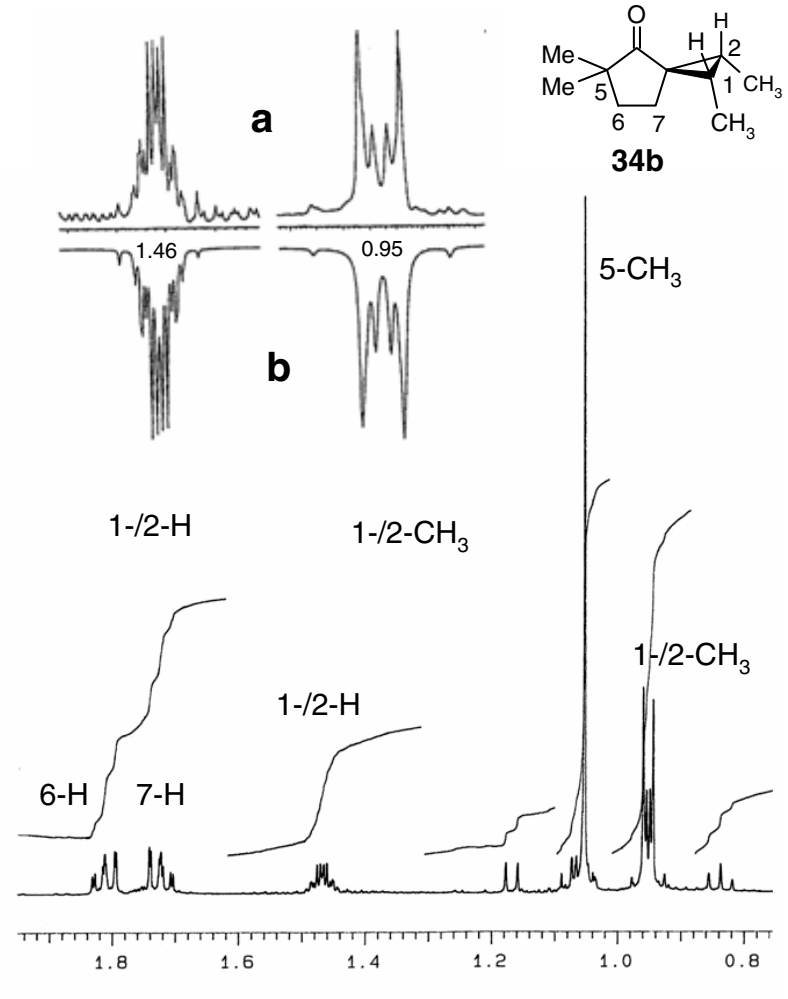
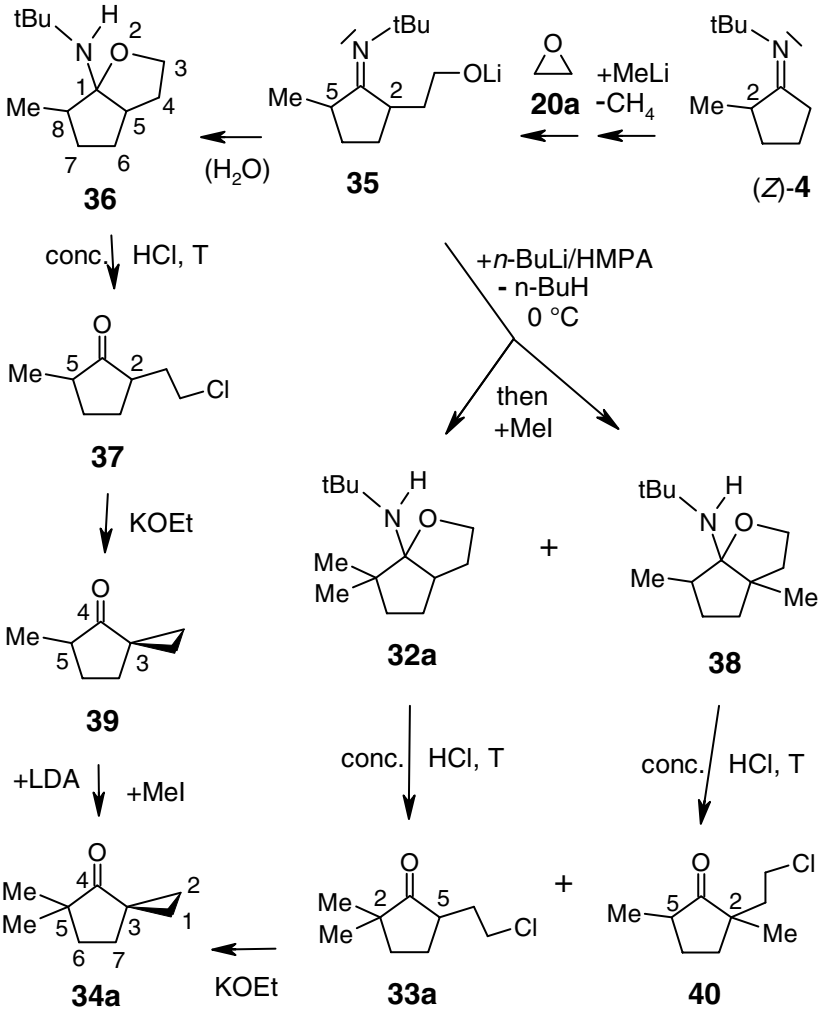


Figure 1. Total ^{1}H NMR (400 MHz) spectrum of **34b**: Multiplets at 0.95 and 1.46 ppm were expanded in the insert (a) for comparison with their negative spectral simulation (b) that established the 1,2-*cis* configuration.

All of the preceding examples described regioselective second alkylation steps of **1**, but only one of them presented regioselectivity with two different iodoalkanes (Scheme 4) on the 2,2-route. We will now show in Scheme 9 that regioselectivity can be achieved with two different electrophiles also on the one-pot 2,5-route as far as *anti* deprotonation by LDA remains the obligatory pathway. The results will then enable us to examine a third alkylation step for its regioselectivity.



Schem 9. LDA-mediated one-pot dialkylation of ketimine **1** via (*Z*)-**4** and **35** affords **37** and **39** regiospecifically, whereas the third deprotonation/alkylation of **35** by *n*-BuLi/HMPA is unselective; Me = methyl, tBu = *tert*-butyl, T = bath temp. 130 °C.

As we know from Section 2.1, the LDA-mediated *anti* deprotonation of (*Z*)-**4** in Scheme 9 must take place before N-inversion converts (*Z*)-**4** into (*E*)-**4**. The temperature (–23 °C) chosen for deprotonating (*Z*)-**4** with LDA/H_3CLi was sufficiently low, as shown by the subsequent alkylation with ethylene oxide (**20a**) which occurred exclusively at the 5-position and formed first the alkoxide **35** and therefrom the two diastereomeric N,O-acetals **36** (ca. 1:1). De-aminating ring cleavage of **36** in boiling conc. HCl (GP4) furnished the two possible dastereomers (3:7) of the γ-chloro ketone **37** as the almost only products. The entailing cyclization (GP5) provided the known[24] monomethyl spiroketone **39**. Subsequent methylation of **39** to give **34a** can be recommended as an emergency tool if **39** showed up as a contamination of **34a** after an incomplete second methylation during the GP2b.

The above regiospecific formation of the alkoxide **35** offered an opportunity to examine a third deprotonation in the one-pot system for its regioselectivity. Having noted that this in-situ operation required HMPA/*n*-BuLi as a base, we learned now by ^{1}H NMR that *n*-BuLi with HMPA was not consumed (no proton transfer from C(5) or C(2)) until the temperature was raised to 0 °C. The two emerging azaallyllithiums (not shown) were trapped with iodomethane, whereupon protolytic work-up generated the isomeric N,O-acetals **32a** and **38** (9:10) but not more than traces of enamines or products that carried C=O or C=N double bonds. Although only a single major diastereomer of **38** could be recognized, the subsequent constitutional confirmation through de-aminating ring cleavage in boiling conc. HCl (GP4) afforded two diastereomers of **40** in the mixture of the γ-chloro ketones **33a** and **40** (43:57). This ratio quantified the regio-unselectivity for the methylation of alkoxide **35**; possible reasons for such a behavior might be an N-inversion of **35** at 0 °C or an intrinsically indiscriminating attitude of the unavoidable base system *n*-BuLi/HMPA. Purification of the two γ-chloroketones **40** was easy because **40** survived the cyclization (GP5) process in a KOH/EtOH solution without substitution or any otherwise imaginable cyclizations, while the accompanying **33a** was cyclized with formation of the more volatile spiro ketone **34a** that was separated through distillation from the higher-boiling γ-chloroketones **40**.

3. Conclusions

(i) Our one-pot procedures were devised on the basis of conditions described[1,2] for 2-iminobutanes. As a comfortrable improvement, the observation of gas (CH_4) evolution from H_3CLi enabled us to perform the LDA-catalyzed deprotonations at or above –40 °C completely within much shorter[2] periods of time. An especially high deprotonation propensity of our iminocyclopentanes may have been helpful to prevent the imminent *E*/*Z* equilibration.

(ii) The following mechanistic peculiarities[1 - 3,8] of ketimine *anti* deprotonation necessitated the application of one-pot methods: The emerging *anti* azaallyllithium species changed quickly into its *syn* configuration; in order to enter the 2,5-route, this *syn* species should be alkylated at or below ca. –70 °C since it will generate a metastable *Z* product. With warming to a maximum of –40 °C, the second deprotonation step had to be performed before the *Z* to *E* stereoinversion would take place. Thus, this kind of kinetic control relied on a prompt treatment of the (*Z*)-product with a trapping agent. At 30 °C, on the other hand, the *Z* product equilibrated with the thermodynamically favored *E* isomer whose *anti* deprotonation and methylation furnished the 2,2-dimethylated product with good (95%) regioselectivity.

(iii) In contrast, the third deprotonation step was unselective with the two bases used in this work: Deprotonation by LDA was slower than N-stereoinversion, while *n*-BuLi/HMPA reacted fast but admitted *syn* deprotonation.

(iv) *Anti* deprotonation was obligatory with the LDA-repellent *N*-tBu group that impeded *syn* deprotonations. Many other bulky *N*-alkyl (but not[5] *N*-aryl) groups at nitrogen might also be suitable, especially the chiral ones.[25,26] Our observations and conclusions were consistent with the results of very instructive kinetic and mechanistic analyses of the regioselective deprotonation and methylation of *N*-alkyliminocyclohexanes.[27]

(v) Trapping of the intermediate azaallyllithiums was fast with iodomethane or ethylene oxide but very slow with *trans*-2,3-dimethyloxirane that reacted stereospecifically. The resultant basic products were always stable in cold, dilute aqueous solution. The NMR spectra of these one-pot products could be interpreted only partially because of cases with complicating asymmetry effects and the presence of basic side-products (sometimes together with enamine isomers). Therefore, reliable product assignments could be achieved only through de-aminating (often uncomfortably

slow) hydrolytic cleavage that afforded methylated cyclopentanones, spiroacetals, a tricyclic acetal (dioxapropellane), or 2-choroethylated cyclopentanones. In order to achieve higher total conversion with volatile and sensitive cleavage products, it may be profitable to perform this de-amination in a distillation apparatus for up to 10 hours. HCl elimination from the γ-chloroketones provided both known and new spiro[2.4]heptan-4-ones via a reasonably short route.

4. Experimental

4.1. General Remarks. All NMR chemical shifts δ were referenced to internal Me_4Si. Abbreviations for NMR spin coupling multiplicities were as follows: d = doublet, m = multiplet, q = quartet, quat = quaternary, qi = quintet, s = singlet, sept = septet, sext = sextet, t = triplet.

4.2. General Procedure 1 (GP1): Monoalkylation of 1. The ketimine **1** (2.78 g, 20.0 mmol) and dry *N*,*N*-diisopropylamine (0.393 mL, 2.8 mmol) were dissolved in anhydrous THF (15 mL) and stirred at –40 °C under argon gas cover. After the dropwise addition of methyllithium (20.0 mmol) in Et_2O (13.8 mL) with brisk evolution of CH_4 gas during 15 min, the deeply yellow solution was cooled at –70 °C and treated with iodomethane (MeI, 1.25 mL, 20.0 mmol), which caused an immediate precipitation of LiI from the weakly yellow solution. The resulting metastable product (*Z*)-**4** was not characterized but was warmed up for the second deprotonation/alkylation step either to –40 °C (2,5-route, GP2a) or to +30 °C (2,2-route, GP2b).

4.3. General Procedure 2 (GP2): Second alkylation of 1. The freshly prepared (GP1) solution of (*Z*)-**4** (nominally 20 mmol) and *N*,*N*-diisopropylamine (2.8 mmol) in THF/Et_2O (39 mL) was used for the two regioselective second alkylations as follows.

4.3.1. GP2a (2,5-route). The stirred (*Z*)-**4** solution was warmed up from –70 °C to –40 °C and without delay titrated with H_3CLi (up to 23 mmol) in Et_2O (ca. 14 mL) during 15 min. The amount of H_3CLi should suffice to consume (*Z*)-**4** completely. The evolution of CH_4 ceased after 12 min, whereupon this orange-colored solution of the azaallyllithium **6** (*syn*) was quenched by the quick addition of the electrophile MeI (1.50 mL, 24.1 mmol at –40 °C) or of an oxirane (at –60 °C). After slow warming to rt, the solution of the dialkylated derivative was either subjected to further deprotonation or worked up as described below in GP2c.

4.3.2. GP2b (2,2-route). The above (*Z*)-**4** solution, as obtained in the GP1, was warmed up quickly and stirred at 30 °C for 2 hours so as to equilibrate (*Z*)-**4** and (*E*)-**4**. The mixture was cooled in an ice-bath and titrated with H_3CLi as long as CH_4 gas was liberated (1.12 equiv within 55 min). This

solution of the created azaallyllithium **11** (*syn*) was cooled and quenched by the quick addition of the electrophile, either MeI (1.2 equiv at –40 °C) or an oxirane (at ≤ –70 °C). After 90 min at rt, the resultant solution of the 2,2-dialkyl derivative was either subjected to further deprotonation or worked up as follows.

4.3.3. GP2c (work-up method). The above solution from GP2a or GP2b (up to 20 mmol of products) was poured onto a mixture of aqueous hydrochlorid acid (2 M, 30 mL) and crushed ice (30 g). The aqueous layer (if sufficiently acidic) should contain the protonated basic products and was shaken with Et_2O (to be discarded), then alkalized with aqueous NaOH (2 M), and extracted with Et_2O (3 ×). These Et_2O extracts were combined, washed with distilled water until neutral, dried over Na_2SO_4, filtered, and concentrated to yield the basic products and accompanying contaminants.

4.4 General Procedure 3 (GP3): De-aminating hydrolysis of the basic products. A sample of the crude mixture of the prepurified basic products (GP2) was dissolved in the 20-fold volume of aqueous H_2SO_4 (2 N) and heated to reflux (double-walled reflux condensor) at 130 °C (bath temp.). After cooling to rt, the condensor was rinsed with Et_2O and distilled water, and the combined aqueous phases were extracted with Et_2O (3 ×). The combined (four) organic phases were washed with distilled water until neutral, dried over Na_2SO_4, filtered, and distilled to separate the volatile ketones from other non-basic compounds. The above acidic aqueous layer was stirred in an ice-bath during alkalization with aqueous NaOH ("30%"), then extracted with Et_2O (3 ×) and discarded. These latter Et_2O extracts were combined, washed with distilled water until neutral, dried over Na_2SO_4, filtered, and concentrated to yield the unconsumed basic products and accompanying contaminants.

4.5. General Procedure 4 (GP4): Reactions in boiling conc. HCl. The prepurified (GP2) basic product fraction was mixed with concentrated hydrochloric acid (2.5 mL per mmol of the expected products) in a round-bottomed flask that carried a double-walled reflux condensor to prevent the volatile compounds from escaping by way of a steam-distillation. The stirred mixture was heated to reflux (bath temp. 130 °C) for at least 1 hour. Any emanating gaseous HCl was diverted toward a neutralizing absorbent. After cooling to rt, the condensor was rinsed with Et_2O and distilled water (2 ×) into the product mixture which was then poured out of the flask with more water and Et_2O. The aqueous layer was shaken with Et_2O (3 ×), and the combined Et_2O phases were washed with distilled water until neutral, dried over Na_2SO_4, filtered, and concentrated at below 40 °C down to a pressure of not less than 70 Torr because some γ-chloro ketones were quite volatile. The crude product may be used for further transformations.

Note: In case of an intended purification, it may be important to remove THF completely from the initially employed material because the cleavage of THF by conc. HCl would generate 1,4-dichlorobutane that may distil together with the γ-chloro ketones.

4.6. General Procedure 5 (GP5): Preparing the spiro[2.4] ketones through HCl elimination. The following doses were calculated per **y** molar equiv of each chloroethyl function of the employed γ-chloro ketone. Solid KOH (0.29y g, 5.17y mmol) was stirred in a round-bottomed flask under inert gas cover and mixed with ethanol (99%, 1.1y mL). The mixture became hot during the complete dissolution of KOH. After cooling in an ice-bath, a solution of the γ-chloro ketone in ethanol (99%, 0.8y mL) was added dropwise within y min and began to precipitate KCl immediately. After further stirring in the closed vessel at rt for 2 hours, the mixture was diluted with distilled water until all KCl was dissolved, whereupon this solution was shaken with pentane (4 ×). The combined organic phases were washed with aqueous Na_2CO_3 (4 ×), dried over Na_2SO_4, filtered, concentrated at 40 °C down to a pressure of not less than 70 Torr, and finally distilled.

4.7. *N*-(Cyclopentylidene)-*tert*-butylamine (1). A round-bottomed, three-necked flask (4 L) was fitted with a strong mechanical stirrer, a two-walled reflux condensor, and a pressure-equalizing dropping funnel (250 mL). The flask was charged with cyclopentanone (112 mL, 1.26 mmol) and anhydrous Et_2O (900 mL), thereafter with *tert*-butylamine (440 mL, 4.21 mol) under argon gas cover. With strong stirring of this mixture at –78 °C, a solution of $TiCl_4$ (72.5 mL, 661 mmol) in dry pentane (600 mL) was added dropwise during 1 hour and began to produce a yellow precipitate immediately. The mixture was warmed up and refluxed for 3 hours, then cooled to rt and filtered. The filter cake was washed with Et_2O until the filtrate became colorless. The combined filtrates were concentrated to give a dark-red oil (134.4 g) that was distilled in a dry Vigreux column. The slightly yellow distillate (88.8 g, 51%) was an oil with b.p. 56 – 62 °C/12 Torr (Ref. [6]: 69 – 70 °C/20 Torr) and consisted of ketimine **1** and its enamine[28] **1A** (82:18).

^{1}H NMR of **1** ([D_6]benzene, 400 MHz) δ 1.27 (s, 9H, tBu), 1.36 (qi, ^3J = 6.9 Hz, 2H, $H_2C(3)$), 1.50 (qi, ^3J = 6.9 Hz, 2H, $H_2C(4)$), 1.94 (t, ^3J = 7 Hz, 2H, $H_2C(2)$), 2.27 (t, ^3J = 7.3 Hz, 2H, $H_2C(5)$) ppm;

^{13}C NMR of **1** ([D_6]benzene, 100.6 MHz) δ 23.5 (tm, ^{1}J = 130 Hz, $H_2C(3)$), 26.5 (tm, ^{1}J = 131 Hz, $H_2C(4)$), 30.3 (qm, ^{1}J = 125 Hz, tBu), 30.9 (obscured t, $H_2C(2)$), 38.8 (tm, ^{1}J = 129 Hz, $H_2C(5)$), 55.4 (> sept, ^{2}J = ca. 4 Hz, Me_3C), 172.9 (broadened qi, ^{3}J = ca. 5.6 Hz, C=N) ppm;

^{1}H NMR of enamine **1A** ([D_6]benzene, 400 MHz) δ 1.17 (s, 9H, tBu), 1.78 (qi, ^{3}J = 7.2 Hz, 2H, $H_2C(4)$), 2.17 (tq, ^{3}J = 7.3 Hz, apparent $J \approx 2$ Hz, 2H, $H_2C(3)$), 2.52 (tq, ^{3}J = 6.9 Hz, apparent $J \approx 2$ Hz, 2H, $H_2C(5)$), 2.78 (broad s, 1H, NH), 4.36 (pseudo-qi, apparent J = ca. 1.9 Hz, 1H, HC(2)), assigned through comparison with **12**;

^{13}C NMR of enamine **1A** ([D_6]benzene, 100.6 MHz) δ 22.2 (obscured tm, ^{1}J = ca. 130 Hz, $H_2C(4)$), 29.1 (obscured qm, ^{1}J = ca. 125 Hz, tBu), 32.5 (tm, ^{1}J = 130 Hz, $H_2C(3)$), 36.5 (broadened td, ^{1}J = 130 Hz, ^{3}J = 8 Hz to 2-H, $H_2C(5)$), 50.4 (m, ^{2}J = ca. 3.7 Hz, Me_3C), 92.9 (broadened dm, ^{1}J = 159 Hz, HC(2)), 143.9 (unresolved, C(1)) ppm, assigned as above.

4.8. *N*-(2-Methylcyclopentylidene)-*tert*-butylamine (4). Upon preparation (GP1) of (*Z*)-**4**, the thermodynamically more stable diastereomer (*E*)-**4** was generated in situ through stirring for 2 hours at 30 °C. Both (*Z*)-**4** and (*E*)-**4** were not characterized but constitutionally confirmed through their common hydrolysis (GP3) product 2-methylcyclopentanone (**9**).

4.9. *N*-(2,5-Dimethylcyclopenten-1-yl)-*tert*-butylamine (7A). The GP2a protocol was used to generate the enamine **7A** from **1** (20 mmol) and to isolate the basic fraction as a yellow oil (3.07 g). This sample contained minor basic contaminants but no ketimine form and no 2,2-dimethyl isomer (**12**).

NMR of enamine **7A** (CCl_4, 400 MHz) δ 0.97 (d, ^{3}J = 6.8 Hz, 3H, 5-CH_3), 1.13 (s, 9H, tBu), 1.49 (s, 3H, 2-CH_3), rest obscured by the contaminants;

^{13}C NMR of enamine **7A** (CCl_4, 100.6 MHz) δ 13.0 (q, 2-CH_3), 18.9 (q, 5-CH_3), 29.5 (t, $H_2C(4)$), 30.8 (q, tBu), 33.3 (t, $H_2C(3)$), 40.4 (d, HC(5)), 51.7 (quat, Me_3C), 114.8 (quat, C(2)), 144.6 (quat, C(1)) ppm.

4.10. 2,5-Dimethylcyclopentanone (8) and 2-methylcyclopentanone (9). The constitution of **7a** and the presence of the monomethyl ketimine **4** (5%) in the above run were determined through de-aminating hydrolysis (GP3, 4 hours) of a sample (2.97 g) in boiling H_2SO_4 (2 N, 44 mL) with final distillation at 20 – 60 °C (bath temp.)/12 Torr: Colorless mixture (775 mg) of the ketones **8** and **9** in the molar ratio of *trans*-**8**/*cis*-**8**/**9** = 60:35:5.

^{1}H NMR of **8** (CCl_4, 400 MHz) δ 1.03 (d, ^3J = 6.8 Hz, 2-/5-CH_3 of *cis*-**8**), 1.07 (d, ^3J = 7.1 Hz, 2-/5-CH_3 of *trans*-**8**) ppm in accord with Refs. [29] and [30];

^{1}H NMR of **9** (CCl_4, 400 MHz) δ 1.04 (d, ^3J = ca. 7 Hz, 2-CH_3) ppm;

^{13}C NMR of *trans*-**8** (CCl_4, 100.6 MHz) δ 14.7 (2-/5-CH_3), 30.1 (H_2C(3)/(4)), 43.1 (HC(2)/(5)), 218.7 (C=O) ppm;

^{13}C NMR of *cis*-**8** (CCl_4, 100,6 MHz) δ 15.2 (2-/5-CH_3), 28.8 (H_2C(3)/(4)), 42.0 (HC(2)/(5)), 219.0 (C=O) ppm in accord with Ref. [30];

^{13}C NMR of **9** (CCl_4, 100.6 MHz) δ 14.2 (2-CH_3), 20.6 (H_2C(4)), 31.9 (H_2C(3)), 36.8 (H_2C(5)), 43.3 (HC(2)), 217.0 (C=O) ppm in accord with Ref. [31] in $CDCl_3$;

4.11. *N*-(2,2-Dimethylcyclopentylidene)-*tert*-butylamine (12). The GP2b protocol was employed to generate (*E*)-**12** from **1** (15.0 mmol). The basic product fraction (2.14 g) contained mainly (*E*)-**12** but not more than a trace of an enamine.

^{1}H NMR (CCl_4, 400 MHz) δ 0.95 (s, 6H, 2 $\times$ 2-CH_3), 1.17 (s, 9H, tBu), 1.52 (t, ^3J = 7 Hz, 2H, H_2C(3)), 1.71 (qi, ^3J = 7.2 Hz, 2H, H_2C(4)), 2.27 (t, ^3J = 7.4 Hz, 2H, H_2C(5)) ppm;

^{13}C NMR (CCl_4, 100.6 MHz) δ 21.7 (t, H_2C(4)), 27.0 (q, 2 $\times$ 2-CH_3), 30.0 (q, tBu), 30.3 (t, H_2C(3)), 38.9 (t, H_2C(5)), 44.0 (quat, C(2)), 54.6 (quat, Me_3C), 176.3 (quat, C=N) ppm;

4.12. 2,2-Dimethylcyclopentanone (13). The constitution of **12** was ascertained by de-aminating hydrolysis (GP3, 4 hours) of a sample (2.00 g) in boiling H_2SO_4 (2 N, 30 mL) and subsequent distillation at 20 – 52 °C (bath temp.)/12 Torr: The ketone mixture (753 mg) consisted of 2,2-dimethyl- (**13**), *trans*- and *cis*-2,5-dimethyl- (**8**), and monomethylcyclopentanone (**9**) in the molar ratio of 92:2:1:3.

^{1}H NMR of **13** ($CDCl_3$, 400 MHz) δ 1.04 (s, 6H, 2 $\times$ 2-CH_3), 1.81 (t, ^3J = 6.8 Hz, 2H, H_2C(3)), 1.90 (qi, ^3J = 7.1 Hz, 2H, H_2C(4)), 2.26 (t, ^3J = 7.6 Hz, 2H, H_2C(5)) ppm in accord with Ref. [32];

^{13}C NMR of **13** ($CDCl_3$, 100.6 MHz) δ 18.7 (t, H_2C(4)), 23.8 (q, 2 $\times$ 2-CH_3), 37.1 (t, H_2C(5)), 38.5 (t, H_2C(3)), 44.9 (quat, C(2)), 223.6 (quat, C=O) ppm in accord with Refs. [29], [32], and [33];

4.13. *N*-(2-Isopropyl-2-methylcyclopentylidene)-*tert*-butylamine (14K) and the enamine *N*-(5-isopropyl-5-methylcyclopenten-1-yl)-*tert*-butylamine (14A). Following the GP1 protocol, the ketimine **1** (20.0 mmol) was methylated to give (*Z*)-**4**. After 2 hours at 30 °C, the generated product (*E*)-**4** was deprotonated (GP2b) by H_3CLi at 0 °C with slow evolution of CH_4 (540 mL, 21.6 mmol in 55 min). The emerging azaallyllithium (*syn*-**11**) was not methylated but instead treated at –40 °C with 2-iodopropane (3.00 mL, 30.0 mmol). After 45 min at rt, the work-up protocol of GP2c (2 M HCl, 60 mL, 60 g of ice) furnished a yellow oil (3.30 g, 75%) that contained the ketimine **14K** and its enamine **14A** (89:11 in CCl_4) but no trace of the 2,5-isomer.

^{1}H NMR of **14K** (CCl_4, 400 MHz) δ 0.72 and 0.85 (2 × d, ^3J = 6.8 Hz, 2 × 3H, 2 diastereotopic isopropyl CH_3), 0.91 (s, 3H, 2-CH_3), 1.18 (s, 9H, tBu), 1.30 and ca. 1.6 (2 × m, 1 + 1H, diastereotopic $H_2C(3)$), 1.62 and 1.73 (2 × m, 1 + 1H, diastereotopic $H_2C(4)$), 1.89 (sept, ^3J = 6.9 Hz, 1H, 2-H), 2.00 (dm, ^2J = 16 Hz, 1H of $H_2C(5)$), 2.45 (dm, ^2J = 16 Hz, 1H of $H_2C(5)$) ppm;

^{13}C NMR of **14K** (CCl_4, 100.6 MHz) δ 17.59 and 17.92 (2 × q, 2 diastereotopic isopropyl CH_3), 21.9 (t, $H_2C(4)$), 24.7 (q, 2-CH_3), 30.0 (q, tBu), 30.7 (t, $H_2C(3)$), 32.2 (t, $H_2C(5)$), 34.1 (d, 2-CH), 50.2 (quat, C(2)), 54.6 (quat, Me_3C), 176.6 (quat, C=N) ppm;

^{1}H NMR of **14A** (CCl_4, 400 MHz) δ 0.80 and 0.86 (2 × d, ^3J = 6.8 Hz, 2 × 3H, 2 diastereotopic isopropyl CH_3), 1.00 (s, 3H, 5-CH_3), 1.23 (s, 9H, tBu), 4.10 (t, ^2J = 2.3 Hz, 1H, 2-H) ppm, rest obscured;

^{13}C NMR of **14A** (CCl_4, 100.6 MHz) δ 17.56 and 17.94 (2 × q, 2 diastereotopic isopropyl CH_3), 25.0 (q, 5-CH_3), 28.4 (t, CH_2), 28.9 (q, tBu), 29.8 (t, CH_2), 33.9 (d, 5-CH), 49.9 (quat, C(5)), 51.8 (quat, Me_3C), 91.8 (d, HC(2)), 147.8 (quat, C(1)) ppm;

IR (film) ν 2966, 2872, 1680 (s, C=N), 1645 (w, C=C), 1460, 1368, 1360, 1228, 1213 cm^{-1}.

See **15** for the constitutional confirmation.

4.14. 2-Isopropyl-2-methylcyclopentanone (15). The acid-catalyzed, de-aminating hydrolysis (GP3) of **14K**/**14A** (3.15 g) with aqueous H_2SO_4 (2 N, 80 mL, 3.5 hours) afforded the known[12,13] ketone **15** but left 1.43 g (45%) of **14K**/**14A** intact. The pure sample of **15** (158 mg) distilled at 95 – 97 °C (bath temp.)/12 Torr (Ref. [12]: 68 – 70 °C/13 Torr).

^{1}H NMR (CCl_4, 400 MHz) δ 0.78 and 0.87 (2 × d, ^3J = 6.8 Hz, 2 × 3H, 2 diastereotopic isopropyl CH_3), 0.92 (s, 3H, 2-CH_3), 1.82 (sept, ^3J = 6.8 Hz, 1H, 2-CH), 1.56, ca. 1.9, 2.02, and 2.22 (6 diastereotopic H of $H_2C(3)/(4)/(5)$) ppm;

^{13}C NMR (CCl_4, 100.6 MHz) δ 17.2 and 18.0 (2 × q, 2 diastereotopic isopropyl CH_3), 18.5 (t, $H_2C(4)$), 20.5 (q, 2-CH_3), 31.5 (t, $H_2C(3)$), 32.2 (d, 2-CH), 37.9 (t, $H_2C(5)$), 50.8 (quat, C(2)), 219.1 (quat, C=O) ppm, assigned through comparison with **13**; IR (film) ν 1736 cm^{-1};

MS (70 eV) m/z (%) 140.1 (M^+, 26). 98.1 (100).

4.15. *N*-(2,2,5-Trimethylcyclopentylidene)-*tert*-butylamine (16). The enamine **7A** was generated (GP2a) from ketimine **1** (5.0 mmol) in THFG/Et_2O (ca. 12 mL) and treated in situ at rt with anhydrous HMPA (0.876 mL, 0.894 g, 5.0 mmol) and then *n*-BuLi (6.0 mmol) in hexane (2.5 mL). The orange-colored solution got a yellow tint withim the next 20 min. After further stirring at rt for 100 min, the mixture was cooled in ice for the addition of iodomethane (0.375 mL, 6.0 mmol). The treatment with *n*-BuLi and then iodomethane was repeated in an unsuccessful attempt to achieve tetramethylation. Work-up according to GP2c furnished a yellow oil (900 mg) as the basic fraction that contained the crude ketimine **16** and only a trace of its enamine; the very small portion of tetramethylation became visible only after hydrolysis (to be seen below).

^{1}H NMR of **16** (CCl_4, 400 MHz) δ 0.91 (s, 3H, 2-CH_3), 1.06 (d, ^3J = 7.3 Hz, 3H, 5-CH_3), 1.07 (s, 3H, 2-CH_3), 1.21 (s, 9H, tBu), 2.83 (pseudo-qi, ^3J = 7.3 Hz, 1H, 5-H) ppm, rest obscured by contaminants;

^{13}C NMR of **16** (CCl_4, 100.6 MHz) δ 19.3 (q, 5-CH_3), 28.7 (q, 2-CH_3), 29.6 (q, 2-CH_3), 30.6 (t, $H_2C(3)$), 31.0 (q, tBu), 35.6 (t, $H_2C(4)$), 35.8 (d, HC(5)), 43.5 (quat, C(2)), 55.4 (quat, Me_3C), 178.7 (quat, C=N) ppm;

4.16. 2,2,5-Trimethylcyclopentanone (17) and the tetramethyl congener. Acid-catalyzed, de-aminating hydrolysis (GP3) of a sample (810 mg) of the above crude product **16** in boiling aqueous H_2SO_4 (2 N, 22 mL, 1 hour) left 416 mg (52%) of **16** intact and afforded a distilled mixture (64 mg) of 2,2,5-trimethyl- (**17**) and 2,2,5,5-tetramethylcyclopentanone (**19**) in a 97:3 ratio with b.p. 40 – 85 °C (bath temp.)/12 Torr. The same ratio and similar results were obtained by the same treatment of the ketimine **12** with HMPA/*n*-BuLi/MeI and entailing hydrolysis under similar conditions.

^{1}H NMR of **17** ($CDCl_3$, 400 MHz) δ 0.98 and 1.07 (2 × s, 3 + 3H, 2 × 2-CH_3), 1.12 (d, ^3J = 6.8 Hz, 3H, 5-CH_3), 1.50 (m, 1H), 1.68 (m, 1H), 1.81 (m, 1H), 2.15 (m, 1H), 2.21 (m, 1H) ppm in accord with Refs. [29] and [34];

^{13}C NMR of **17** ($CDCl_3$, 100.6 MHz) δ 15.3 (q, 5-CH_3), 24.1 and 24.8 (2 × q, 2 × 2-CH_3), 28.0 (t, $H_2C(4)$), 36.5 (t, $H_2C(3)$), 43.3 (d, HC(5)), 44.9 (quat, C(2)), 225.0 (quat, C=O) ppm in accord with Refs. [33] and [34];

^{1}H NMR of **19** ($CDCl_3$, 400 MHz) δ 1.05 (s) ppm; ^{13}C NMR of **19** ($CDCl_3$, 100.6 MHz) δ 24.9 (q, 2,2,5,5-CH_3), 34.9 (t, $H_2C(3)/(4)$), 45.3 (quat, C(2)/C(5)) ppm in accord with Ref. [33].

4.17. 2,5-Bis(2-hydroxyethylation) of ketimine 1 to give the N,O-acetal 1-*tert*-butylamino-8-(2-hydroxyethyl)-2-oxabicyclo[3.3.0]octane (24a). A dry three-necked flask (1 L) was charged with the ketimine **1** (27.82 g, 200 mmol), anhydrous THF (200 mL), dry *N*,*N*-diisopropylamine (3.93 mL, 27.9 mmol), and a strong magnetic stirring bar. This solution was cooled to –60 °C under argon gas cover and treated with a stock solution (4.08 M, 147 mL) of ethylene oxide (600 mmol) in THF. Methyllithium (420 mmol) in Et_2O (280 mL) was added dropwise with rapid stirring at –47 °C during 3 hours. The stirred mixture was warmed up to rt (1 hour) and then protonated with distillled water (100 mL). The aqueous layer was shaken with Et_2O (3 ×), and all four organic phases were combined and washed with aqueous Na_2CO_3 (2 N, 3 ×), then dried over Na_2SO_4, filtered, and evaporated to leave an orange-colored, viscous oil (48.32 g) that solidified partially (ca. one half). Recrystalllization from cyclohexane afforded small, colorless blocks of **24a** with m.p. 67.2 – 68.1 °C. A solution of these crystals in CH_2Cl_2 or in CCl_4/$CDCl_3$ (2:1) contained two diastereomeric N,O-acetals (ca. 1:1, *cis* and *trans*?) whose NMR spectra could not be disentangled but displayed no C=O or C=N resonances.

IR (KBr) ν 3394 (s, narrow, O–H), 3347 (w, very sharp N–H), 2956, 2920 (w), 2881, 1520 (w), 1480 (w), 1456 (w), 1362, 1352, 1231 (s), 1050 (s), 1013 (s) cm^{-1}, no C=O and no C=N vibrations. Anal. calcd for $C_{13}H_{25}NO_2$ (227.35): C, 68.68; H, 11.08; N, 6.16. Found: C, 68.91; H, 10.87; N, 6.07.

4.18. The N,O-acetal 24b formed by dialkylation with *trans*-2,3-dimethyloxirane (20b). The ketimine **1** (2.10 g, 15.1 mmol), dry HMPA (2.01 mL, 2.05 g, 11.5 mmol), anhydrous THF (15 ml), and a magnetic stirring bar were placed in a three-necked, round-bottomed flask (100 mL) that was fitted with a dry reflux condensor that was connected to a gas burette. The rapidly stirred solution was cooled to –42 °C during the dropwise addition of H_3CLi (ca. 15 mmol) in Et_2O (ca. 10 mL), which liberated CH_4 (375 mL, 15.0 mmol) at first instantly and the last fifth within 10 min. The yellow solution was cooled to –72 °C and treated with *trans*-2,3-dimethyloxirane (**20b**, 4.24 mL, 47.3 mmol). The colorless solution was warmed to 0 °C and titrated again with H_3CLi: The generation of CH_4 continued up to rt until deprotonation of the monoalkylated intermediate **4** and of unconsumed

oxirane **20b** (ca. 30 mmol)[22] was complete. The resultant yellow solution was treated with another portion of **20b** (47.3 mmol) and heated at a dry-ice-cooled condensor at 56 °C for 2 hours with gradual decolorization. The acidic work-up protocol of GP2c furnished the basic product fraction (3.52 g) as a viscous, yellow oil whose NMR spectra were too complicated for an instructive analysis; therefore, the constitution of **24b** was ascertained through de-aminatig ring cleavage as described for **25b**.

4.19. (3aα,5aβ)-Octahydrocyclopenta[1,2-b;1,5-b´]difuran (25a). This known[16] bridged spiroacetal was obtained through acid-catalyzed, de-aminating hydrolysis (GP3, 2 hours) of **24a** with boiling aqueous H_2SO_4 (2 N). After work-up, it distilled as a colorless liquid with b.p. 143 – 148 °C (bath temp.)/70 Torr (Ref. [16]: 155 – 160 °C (bath temp.)/70 Torr).

^{1}H NMR (CCl_4, 80 MHz): As in Ref. [16]; ^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 31.14 ($2 \times CH_2$), 31.50 ($2 \times CH_2$), 47.7 ($2 \times CH$), 69.2 ($2 \times OCH_2$), 128.8 ppm ($1 \times$ quat C) as in Ref. [16]. Anal. calcd for $C_9H_{14}O_2$ (154.2): C, 70.10; H, 9.15. Found: C, 69.58; H, 9.24.

4.20. (3aα,5aβ)-2,3,6,7-Tetramethyloctahydrocyclopenta[1,2-b;1,5-b´]difuran (25b). A portion (3.37 g) of the crude N,O-acetal **24b** was de-aminated (GP4, 3.5 hours) in boiling conc. HCl which yielded a non-basic oil (2.08 g) whose distillation afforded the bridged spiroacetal **25b** (1.14 g, 36%). Analytically pure **25b** had b.p. 60 – 65 °C (bath temp.)/0.001 Torr and exhibited C_2-symmetry according to the ^{13}C NMR data.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, ^3J = ca. 7 Hz, 6H, 3-/6-CH_3), 1.18 (d, ^3J = 6.6 Hz, 6H, 2-/7-CH_3), 1.45 (m, $2 \times$ 1H, 4-/5-H), 1.87 (sext, ^3J = ca. 6.6 Hz, 2H, 3-/6-H), 1.94 (m, $2 \times$ 1H, second 4-/5-H), 2.06 (m, 2H. 3a-/5a-H), 4.11 (qi, ^3J = ca. 6.6 Hz, 2H, 2-/7-H) ppm, assigned through DQCOSY, NOESY, and HETCOR;

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.9 (q, 3-/6-CH_3), 16.3 (q, 2-/7-CH_3), 28.2 (t, H_2C(4)/(5)), 41.1 (d, HC(3)/(6)), 55.4 (d, HC(3a)/(5a)), 78.2 (d, HC(2)/(7)), 126.9 (quat, C(9)) ppm, assigned through DEPT and HETCOR;

IR (film) ν 2963, 2935, 2872, 1460, 1379, 1116, 1097, 1063, 1052, 991, 960 cm^{-1}.

Anal. calcd for $C_{13}H_{22}O_2$ (210.3): C, 74.24; H, 10.54. Found: C, 74.39; H, 10.44.

4.21. 2,5-Bis(2-chloroethyl)cyclopentanone (26). The crude N,O-acetal **24a** (48.32 g, ≤ 200 mmol) was heated (GP4) in boiling conc. HCl (500 mL) for 2.5 hours. After work-up according to GP4, the brown oil (35.92 g, 86%) was distilled (2 ×) at 110 – 115 °C (bath temp.)/10^{-5} Torr to give **26** as a colorless liquid[18] with an intense odor of pine and a *trans*/*cis* ratio of 4:1.

^{1}H NMR of *trans* and *cis* **26** (CCl_4, 400 MHz) δ 1.47, 1.67, 1.72, 2.09, 2.19, 2.26, and 2.42 (7 × m, 10H), 3.58 and 3.68 (2 × m, 4H, 2 × CH_2Cl) ppm;

^{13}C NMR of *trans* **26** (CCl_4, 100.6 MHz) δ 27.6 (tm, ^1J = 131 Hz, 2-/5-CH_2), 33.2 (broadened t, ^1J = 129 Hz, H_2C(3)/(4)), 42.6 (tm, ^1J = 150 Hz, 2 × CH_2Cl), 46.2 (dm, ^1J = 124 Hz, HC(2)/(5)), 217.3 (quat, C=O) ppm;

^{13}C NMR of *cis* **26** (CCl_4, 100.6 MHz) δ 26.6 (tm, ^1J = 130 Hz, 2-/5-CH_2), 33.3 (obscured t, H_2C(3)/(4)), 42.5 (obscured tm, ^1J = ca. 150 Hz, 2 × CH_2Cl), 45.0 (obscured dm, ^1J = ca. 125 Hz, HC(2)/(5)), 217.3 (quat, C=O) ppm;

IR (film) ν 2963, 2870, 1732 (s), 1451, 1432, 1160, 652 cm^{-1}.

Anal. calcd for $C_9H_{14}Cl_2O$ (209.1): C, 51.69; H, 6.75. Found: C, 52.49; H, 6.95.

4.22. Dispiro[2.1.2.2]nonan-4-one (27). This known[20,21] dispirocyclopentanone was prepared according to GP5 but under mild reflux as reported in Ref. [19].

^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 and 1.16 (2 × pseudo-qi, apparent J = 3.3 Hz, 2 × 4H, 2 × 1-/2-/6-/7-H), 2.10 (s, 4H, H_2C(8)/(9)) ppm;

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.4 (sharp t, ^1J = 164.0 Hz, H_2C(1)/(2)/(6)/(7) of the cyclopropane part), 29.8 (tm, ^1J = 132.0 Hz, H_2C(8)/(9)), 30.0 (quat, C(2)/(5)), 218.9 (quat, C=O) ppm;

4.23. 2,8-Dioxatricyclo[3.3.3.0^{1,5}]undecane (29). The ketimine **1** (0.974 g, 7.0 mmol), dry *N*,*N*-diisopropylamine (0.138 mL, 0.98 mmol), and a stock solution (4.88 mL) of ethylene oxide (**20a**, 21.0 mmol) were dissolved in anhydrous THF (7.0 mL). The rapidly stirred solution was heated to 41 °C under inert gas cover and titrated with H_3CLi in Et_2O, which liberated 355 mL (14.2 mmol) of methane. The work-up protocol GP2c afforded a viscous mixture (1.07 g, ≤ 67%) of **24a** and the corresponding 2,2-isomer (protonated **28**) that was treated with boiling conc. HCl (GP4) and

furnished the dioxapropellane **29** (208 mg) with b.p. 102 – 112 °C (bath temp.)/12 Torr as a colorless liquid.

^{1}H NMR (CCl_4, 80 MHz) δ 1.66 (broadened quasi-s, 10H, 2 × CH and 4 × CH_2), 3.71 (m, 4H, 2 × OCH_2) ppm;

^{13}C NMR ($CDCl_3$, 20.15 MHz) δ 34.2, 35.8, and 37.7 (3 × t, H_2C(9)/(10)/(11)), 39.4 (t, H_2C(4)/(6)), 58.5 (quat, C(5)), 68.2 (t, OH_2C(3)/(7)), 127.7 (quat, C(1)) ppm;

Anal. calcd for $C_9H_{14}O_2$ (154.2): C, 70.10 ; H, 9.15. Found : C, 69.58 ; H, 9.24.

4.24. 1-*tert*-Butylamino-8,8-dimethyl-2-oxabicyclo[3.3.0]octane (32a). The protocol of GB2b was followed for the twofold deprotonatio and methylation of ketimine **1** (2.78 g, 20.0 mmol) that afforded (*E*)-**12** and methane (500 and 532 mL) at –40 °C. The stirred solution was kept at –40 °C during the addition of HMPA (1.48 mL, 8.43 mmol) and then of *n*-BuLi (24.0 mmol) in hexane (9.60 mL). After stirring at rt for 2 hours, the solution was cooled again to –40 °C, treated with a stock solution (10.2 mL) of ethylene oxide (40.0 mmol) in THF, and kept in a bath of 30 °C for 60 min. The red solution was worked up (GP2c) to give a faintly yellow oil (4.38g) as the basic product fraction that contained mainly one diastereomer of the N,O-acetal **32a**. The constitution of **32a** was confirmed below through conversion into **33a**.

^{1}H NMR (CCl_4, 400 MHz) δ 0.90 (s, 3H, 1 × 8-CH_3), 0.97 (s, 3H, 1 × 8-CH_3), 1.12 (s, 9H, tBu), 1.48, 1.55, 2.06, 2.37, 2.53, and 3.65 (6 × m, 6 × ca. 1H), 3.98 (td, ^3J = 8.5 Hz, ^4J = 2 Hz, 1H) ppm, rest obscured;

^{13}C NMR (CCl_4, 100.6 MHz) δ 22.7 (qm, ^1J = 124 Hz, 8-CH_3), 26.0 (qm, ^1J = 124 Hz, second 8-CH_3), 30.3 (obscured tm, ^1J = ca. 122 Hz, CH_2), 32.1 (qm, ^1J = 125 Hz, tBu), 35.4 (tm, ^1J = 128 Hz, CH_2), 39.6 (tm, ^1J = 128 Hz, CH_2), 46.0 (broadened dm, ^1J = 135 Hz, HC(5)), 48.3 (narrow m, C(8)), 49.9 (> sext, apparent J = 3.8 Hz, Me_3C), 67.5 (tm, ^1J = 144.5 Hz, H_2C(3)), 108.3 (quat, C(1)) ppm;

IR (CCl_4) ν 2959, 2869, 1462, 1362, 1222 cm^{-1}.

4.25. 5-(2-Chloroethyl)-2,2-dimethylcyclopentanone (33a). The above N,O-acetal **32a** (4.29 g, ≤ 19.6 mmol) was de-aminated by boiling conc. HCl (GP4, 2 hours), which afforded the crude γ-chloro ketone **33a** (2.78 g, almost 80%) as a slightly yellow oil. The analytically pure, colorless liquid (2.39 g, 69% yield with respect to **1**) had b.p. 69 – 71 °C/0.001 Torr.

^{1}H NMR (CCl_4, 400 MHz) δ 0.95 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.53, 1.68, 1.70, 1.82, and 2.33 (5 × m, 5 × 1H), 2.17 (m, 2H), 3.57 and 3.66 (2 × m, 1 + 1H, CH_2Cl) ppm;

^{13}C NMR (CCl_4, 100.6 MHz) δ 23.9 (qsext, ^1J = 127.5 Hz, ^3J = 5.0 Hz, 2-CH_3), 24.7 (qqi, ^1J = 127.5 Hz, ^3J = 5.1 Hz, second 2-CH_3), 25.8 (tm, ^1J = 130 Hz, 5-CH_2), 33.8 (tm, ^1J = 130 Hz, H_2C(4)), 36.5 (broadened t, ^1J = 130 Hz, H_2C(3)), 42.6 (tq, ^1J = 150 Hz, apparent J = 4.4 Hz, CH_2Cl), 44.6 (pseudo-sext, apparent J = 3.7 Hz, C(2)), 45.6 (d, ^1J = 125 Hz, HC(5)), 220.3 (quat, C=O) ppm, assigned through comparison with **26**;

IR (film) ν 2962, 2869, 1733, 1455, 1381, 1070, 719, 651 cm^{-1}.

Anal. calcd for $C_9H_{15}ClO$ (174.67): C, 61.89; H, 8.66., Found: C, 62.63; H, 8.67.

4.26. 5,5-Dimethylspiro[2.4]heptan-4-one (34a). *a) From **33a**:* The above γ-chloro ketone **33a** (850 mg, 4.87 mmol) was cyclized (GP5) to afford the distilled spiro ketone **34a** (398 mg, 59%). Analytically pure **34a** had b.p. 54.5 – 55 °C/12 Torr.

^{1}H NMR (CCl_4, 400 MHz) δ 0.76 (pseudo-q, 2H, 1-/2-H), 1.04 (s, 6H, 2 × 5-CH_3), 1.05 (obscured m, 2H, second 1-/2-H), 1.84 (t, ^3J = 6.7 Hz, 2H, H_2C(6)), 1.93 (t, ^3J = 6.7 Hz, 2H, H_2C(7)) ppm, assigned through comparison with **27**;

^{13}C NMR (CCl_4, 100.6 MHz) δ 17.2 (broadened t, ^1J = 164 Hz, H_2C(1)/(2)), 23.8 (qsext, ^1J = 127.0 Hz, ^3J = 4.6 Hz, 2 × 5-CH_3), 27.4 (quat, C(3)), 28.3 (tm, ^1J = 132 Hz, H_2C(7)), 36.7 (tsept, ^1J = 131 Hz, H_2C(6)), 45.5 (m, apparent J = 3.5 Hz, C(5)), 218.9 (unresolved, C=O) ppm, assigned through comparison with **27** and **33a**;

IR (film) ν 3083 (w), 2961, 2869, 1728 (s), 1346, 1050, 1009 cm^{-1}.

Anal. calcd for $C_9H_{14}O$ (138.21): C, 78.21; H, 10.21., Found: C, 78.30; H, 10.27.

*b) From 5-methylspiro[2.4]heptan-4-one **(39)***: A three-necked, round-bottomed flask (250 mL) was charged with *N*,*N*-diisopropylamine (4.00 mL, 2.87 g, 28.3 mmol) in anhydrous THF (64 mL), cooled to –65 °C, and treated with H_3CLi (28.3 mmol) in Et_2O (19.5 mL) within 10 min under argon cover gas. After the brisk CH_4 evolution and subsequent cooling at –78 °C, a solution of the distilled ketone **39** (2.95 g, 25.7 mmol) in anhydrous THF (25.7 mL) was slowly added dropwise. The mixture became yellow on subsequent stirring at –35 °C for 30 min, whereupon it was re-cooled to –78 °C and treated with iodomethane (1.91 mL, 4.35 g, 30.5 mmol). After slow warming to rt (2 hours), the

mixture was diluted with distilled water (50 mL) and shaken with pentane (3 × 50 mL). The combined pentane extracts were washed with aqueous Na_2CO_3 (2 N, 3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated to yield practically pure **34a** (2.23 g, 63%). Alternatively, solid KH was used as the base in place of LDA to provide **34a** (crude yield 66%).

4.27. 1,2,5,5-Tetramethylspiro[2.4]heptan-4-one (34b). The ketimine **1** was dimethylated (GP2b) to give (*E*)-**12** that was deprotonated with HMPA/*n*-BuLi and then alkylated by *trans*-2,3-dimethyloxirane (**20b**). The resultant, intricate mixture of basic products was de-aminated (GP4), then cyclized (GP5) and prepurified by distillations and column chromatography. The samples obtained from several runs were combined (941 mg) and distilled at 100 – 105 °C (bath temp.)/12 Torr to afford the pure spiro ketone **34b** (519 mg) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 400 MHz, Figure 1) δ 0.95 (m, 6H, AA´ part of an $A_3A'_3XX'$system, 1-/2-CH_3), 1.05 (s, 6H, 2× 5-CH_3), 1.46 (m, 2H, XX´ part, 1-/2-H), 1.73 (tm, ^3J = ca. 6.8 Hz, 2H, $H_2C(7)$), 1.81 (tm, ^3J = ca. 6.8 Hz, 2H, $H_2C(6)$) ppm, assigned through the NOESY correlations 5-CH_3 ↔ $H_2C(6)$ ↔ $H_2C(7)$ ↔ 1-/2-CH_3 and comparison with **34a**;

^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 8.1 (q, 1-/2-CH_3), 19.0 (t, $H_2C(7)$), 23.8 (q, 2 × 5-CH_3), 26.3 (d, HC(1)/(2)), 36.1 (quat, C(3)), 36.8 (t, $H_2C(6)$), 45.9 (quat, C(5)), 223.0 (quat, C=O) ppm, assigned through HETCOR, DEPT, and COLOCS(8 Hz);

IR (film) ν 2998 (w), 2959, 2869, 1721 (s), 1462, 1104, 1085 cm^{-1}.

Anal. calcd for $C_{11}H_{18}O_2$ (166.26): C, 79.47; H, 10.91. Found: C, 79.68; H, 11.05.

4.28. 1-*tert*-Butylamino-8-methyl-2-oxabicyclo[3.3.0]octane (36). The protocol of GP2b was followed for the deprotonation and alkylation of **1** (13.92 g, 100 mmol), using MeI (6.24 mL, 100 mmol) for the first alkylation. The second deprotonation was carried out by the slow (1 mL per min) addition of H_3CLi (100 mmol) at –23 °C, followed by a stock solution (37.5 mL) of ethylene oxide (**20a**, 150 mmol) in THF at –78 °C. The immediately decolorized mixture was stirred at rt, then diluted with distilled water and extracted with Et_2O (3 ×). The combined organic phases were washed with aqueous Na_2CO_3 (2 N, 3 ×), dried over Na_2SO_4, filtered, and concentrated. The THF-containing residue was dried for 12 hours under 12 Torr in the presence of P_4O_{10}. The remaining orange-colored oil (19.51 g) contained mainly two diastereomeric N,O-acetals (1:1) and displayed

only traces of C=N and C=O absorptions in the IR and ^{13}C NMR spectra. The constitution of **36** was confirmed below by two derivatives (**37** and **39**).

^{1}H NMR of **36** (CCl_4, 400 MHz) δ 0.88 (d, ^{3}J = 7.2 Hz, 3H, 8-CH_3), 0.96 (d, ^{3}J = 6.8 Hz, 3H, second 8-CH_3), 1.14 (s, 9H, tBu), 1.15 (s, 9H, second tBu), 3.69, 3.77, and 3.84 (3 × m, 4H, 2 × OCH_2) ppm, rest obscured by minor contaminants;

^{13}C NMR of **36** (CCl_4, 100.6 MHz) δ 14.1 (8-CH_3), 17.2 (second 8-CH_3), 28.6 (CH_2), 31.4 (CH_2), 31.6 (tBu), 31.9 (second tBu), 32.2, 33.5, 33.9, and 34.1 (4 × CH_2), 42.7, 46.0, 48.6, and 49.5 (4 × CH), 50.6 (quat, Me_3C), 50.8 (second quat, Me_3C), 66.0 (H_2C(3)), 66.9 (second H_2C(3)), 106.4 (quat, C(1)), 108.2 (quat, second C(1)) ppm;

IR (film) ν 2957, 2870, 1675 (w), 1362, 1249, 1224 cm^{-1}.

The constitution of this diastereomeric pair was confirmed as follows.

4.29. 2-(2-Chloroethyl)-5-methylcyclopentanone (37). The crude N,O-acetals **36** (19.51 g, ≤ 100 mmol) were de-aminated in boiling conc. HCl (GP4, 2 hours). The extracted, non-basic material was dried under 12 Torr in the presence of solid KOH and paraffin wax for 12 hours and provided crude **37** as a brown oil (11.3 g). The analytically pure sample had b.p. 38.5 – 39 °C/0.06 Torr and consisted of the *trans* and *cis* (7:3) diastereomers exclusively.

^{1}H NMR (CCl_4, 400 MHz) δ 1.03 (d, ^{3}J = 7.2 Hz, 0.87H, 5-CH_3 *cis* to 2-CH_2), 1.08 (d, ^{3}J = 7.0 Hz, 2.13H, 5-CH_3 *trans*), 1.42, 1.61, 1.69, 2.07, 2.16, 2.21, and 2.34 (7 × m, 8H), 3.58 and 3.66 (2 × m, CH_2Cl) ppm;

^{13}C NMR of *trans*-**37** (CCl_4, 100.6 MHz) δ 14.5 (qt, ^{1}J = 127.5 Hz, 5-CH_3), 27.7 (t, ^{1}J = 129 Hz, 2-CH_2), 29.9 (tm, ^{1}J = 132 Hz, H_2C(4)), 33.4 (t, ^{1}J = 128 Hz, H_2C(3)), 42.7 (t, ^{1}J = 151 Hz, CH_2Cl), 43.5 (obscured d, ^{1}J = ca. 123 Hz, HC(5)), 45.8 (d, ^{1}J = 124.5 Hz, HC(2)), 218.4 (quat, C=O) ppm;

^{13}C NMR of *cis*-**37** (CCl_4, 100.6 MHz) δ 15.2 (qm, ^{1}J = 128 Hz, 5-CH_3), 26.5 (obscured t, ^{1}J = 129 Hz, 2-CH_2), 28.8 (obscured t, ^{1}J = 129 Hz, H_2C(4)), 33.4 (t, ^{1}J = 128 Hz, H_2C(3)), 42.0 (obscured d, ^{1}J = ca. 127 Hz, HC(5)), 42.6 (obscured t, ^{1}J = ca. 151 Hz, CH_2Cl), 45.0 (d, ^{1}J = 124.5 Hz, HC(2)), 218.6 (quat, C=O) ppm;

IR (film) ν 2963, 2934, 2873, 1738, 1456, 1159 cm^{-1}.

Anal. calcd for $C_8H_{13}ClO$ (160.6): C, 59.81; H, 8.16. Found: C, 60.33; H, 8.28.

4.30. 1-*tert*-Butylamino-5,8-dimethyl-2-oxabicyclo[3.3.0]octane (38) coming along with 32a. The ketimine **1** (2.78 g, 20.0 mmol) was transformed into the alkoxide **35** as descibed above for **36**. Since **35** had been formed with immediate decolorization of the yellow solution at –78 °C, a third deprotonation was begun forthwith at –60 °C: After the addition of HMPA (1.48 mL, 8.43 mmol) and then *n*-BuLi (24.0 mmol) in hexane (9.60 mL), the stirred solution had to be warmed up to 0 °C until the characterstic ^{1}H NMR triplet of *n*-BuLi disappeared within 45 min. The yellow mixture was recooled to –60 °C and treated with iodomethane (2.49 mL, 5.68 g, 40.0 mmol). The immediately decolorized, clear solution was warmed to rt and worked up with ice and dilute acid (GP2c) to yield a faintly yellow oil (3.82 g, crude yield ≤ 90%) that contained the two N,O-acetals **32a** and **38** (ca. 9:10). A less populated, second diastereomer of **38** could not be found among other minor contaminants.

^{1}H NMR of **38** (CCl_4, 400 MHz) δ 1.14 (s, 9H, tBu) ppm, rest obscured;

^{13}C NMR of **38** (CCl_4, 100.6 MHz) δ 14.7 (q, 8-CH_3), 25.2 (q, 5-CH_3), 31.8 (t, CH_2), 32.4 (q, tBu), 39.1 (t, CH_2), 41.1 (t, CH_2), 44.5 (d, HC(8)), 50.5 (quat, Me_3C), 52.0 (quat, C(5)), 65.3 (t, H_2C(3)), 105.2 (quat, C(1)) ppm;

4.31. 5-Methylspiro[2.4]heptan-4-one (39). The crude γ-chloro ketone **37** (9.97 g, ≤ 62 mmol) was cyclized (GP5) to afford a brown oil (8.20 g) whose distillation furnished the almost pure, colorless spiro ketone[24] **39** (4.39 g, ≥ 57%). Redistillation (2 ×) yielded the analytical sample with b.p. 53.0 – 53.5 °C/12 Torr.

^{1}H NMR (CCl_4, 400 MHz) δ 0.75, 0.78, 0.98, and ca. 1.09 (4 × m, 4 × 1H, 2 × 1-/2-H), 1.08 (d, ^3J = 6.7 Hz, 3H, 5-CH_3), 1.58 (m, 1H, 5-H), 1.76 (m, 1H, 6-H), 2.09 (m, 1H, second 6-H), 2.25 (m, 2H, H_2C(7)) ppm;

^{13}C NMR (CCl_4, 100.6 MHz) δ 14.5 (qt, ^1J = 127.0 Hz, 5-CH_3), 15.0 (tm, ^1J = 163 Hz, H_2C(1) or (2)), 19.0 (tqi, ^1J = 165 Hz, H_2C(2) or (1)), 28.3 (quat, C(3)), 29.9 (broadened t, ^1J = 131 Hz, H_2C(7)), 30.1 (tm, ^1J = 130 Hz, H_2C(6)), 44.0 (dt, ^1J = 124.7 Hz, HC(5)), 216.9 (quat, C=O) ppm, assigned through comparison with **34a**;

IR (film) ν 3088 (w), 2963, 2933, 2870, 1726 (s), 1454, 1350, 1285, 1071, 1029, 1010 cm^{-1}.

Anal. calcd for $C_8H_{12}O$ (124.2): C, 77.38; H, 9.74., Found: C, 77.44; H, 9.65.

4.32. 2-(2-Chloroethyl)-2,5-dimethylcyclopentanone (40). The above mixture of N,O-acetals **32a** and **38** (3.64 g, ≤ 17.2 mmol) was de-aminated with boiling conc. HCl (GP4, 2.5 hours) to produce a mixture of **33a** and **40** (43:57) as a faintly brown oil (2.53 g). The whole distillable portion (1.99 g, 60% yield with respect to **1**) of this mixture (1:1) had b.p. 67 – 68 °C/0.001 Torr and contained **33a** along with two diastereomers of **40** (CH_3 groups *trans*/*cis* = 2:3). A sample of pure *trans*- and *cis*-**40** was obtained through GP5 since **40** cannot be cyclized whereas **33a** formed the more volatile 5,5-dimethyl spiro ketone **34a** that distilled in the forerun ahead of unchanged **40**.

^{1}H NMR of **40** (CCl_4, 400 MHz) δ 0.97/1.06 (2 × s, *cis*/*trans* 2-CH_3), 1.09/1.08 (2 × d, ^3J = ca. 6.8 Hz, *cis*/*trans* 5-CH_3), 3.41, 3.45, and ca. 3.54 (3 × m, CH_2Cl) ppm, rest obscured;

^{13}C NMR of *cis*-**40** (CCl_4, 100.6 MHz) δ 14.9 (5-CH_3), 21.7 (2-CH_3), 28.0 (2-CH_2), 34.1 (CH_2), 39.9 (CH_2), 40.6 (CH_2), 43.3 (HC(5)), 47.2 (quat, C(2)), 219.6 (quat, C=O) ppm;

^{13}C NMR of *trans*-**40** (CCl_4, 100.6 MHz) δ 15.0 (5-CH_3), 22.6 (2-CH_3), 27.9 (2-CH_2), 34.5 (CH_2), 39.7 (CH_2), 39.8 (CH_2), 42.1 (HC(5)), 47.2 (quat, C(2)), 219.8 (quat, C=O) ppm;

IR (film) ν 2963, 2871, 1736 (s), 1456, 1071 (w) cm^{-1}.

Anal. calcd for $C_9H_{15}ClO$ (174.67): C, 61.89; H, 8.66. Found: C, 61.89; H, 8.61.

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