JOC Article

Domino "Staudinger/Semi-Aza-Wittig/Fragmentation" Reactions of γ-Azido-β-hydroxyketones

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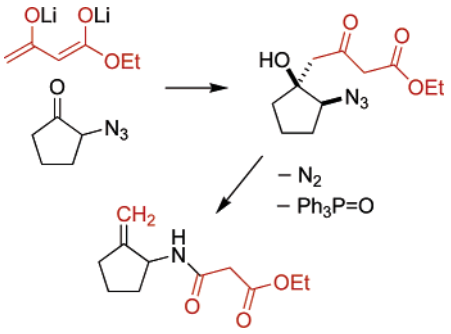

Treatment of γ-azido-β-hydroxyketones with triphenylphosphine resulted, depending on the structural features of the starting materials, in a domino "Staudinger/semi-aza-Wittig/fragmentation" reaction rather than a normal aza-Wittig reaction. 2-Azido-1-hydroxy-1-(2,4-dioxoalkyl)cyclopentanes, readily available by condensation of 1,3-dicarbonyl dianions with 2-azidocyclopentanone, proved to be optimal starting materials for these reactions which afforded 1-(1,3-dioxoalkyl)amino-2-(alkylidene)cyclopentanes.

Introduction

Organic azides represent versatile synthetic building blocks.[1] The formation of iminophosphoranes by reaction of triphenylphosphine (PPh_3) with azides (Staudinger reaction)[2] has been widely used for the synthesis of primary amines,[2,3] imines, and various nitrogen heterocycles.[4] For example, pyrroles have been prepared by reaction of α-azidoketones with 1,3-dicarbonyl dianions,[5] of α-azidoketals with silyl enol ethers,[6] of 2-azido-1,1-dimethoxyethane with 1,3-bis-silyl enol ethers,[7] and of 2-azido-1,1-dimethoxyethane with 1,3-diketones.[8] Reactions of iminophosphoranes with other functional groups have also been reported. This includes, for example, PPh_3 mediated reactions of organic azides with epoxides,[9] alcohols,[10] phthalic anhydride,[11] and carboxylic acids.[12] In the course of our interest in the development of new cyclization reactions of free and masked

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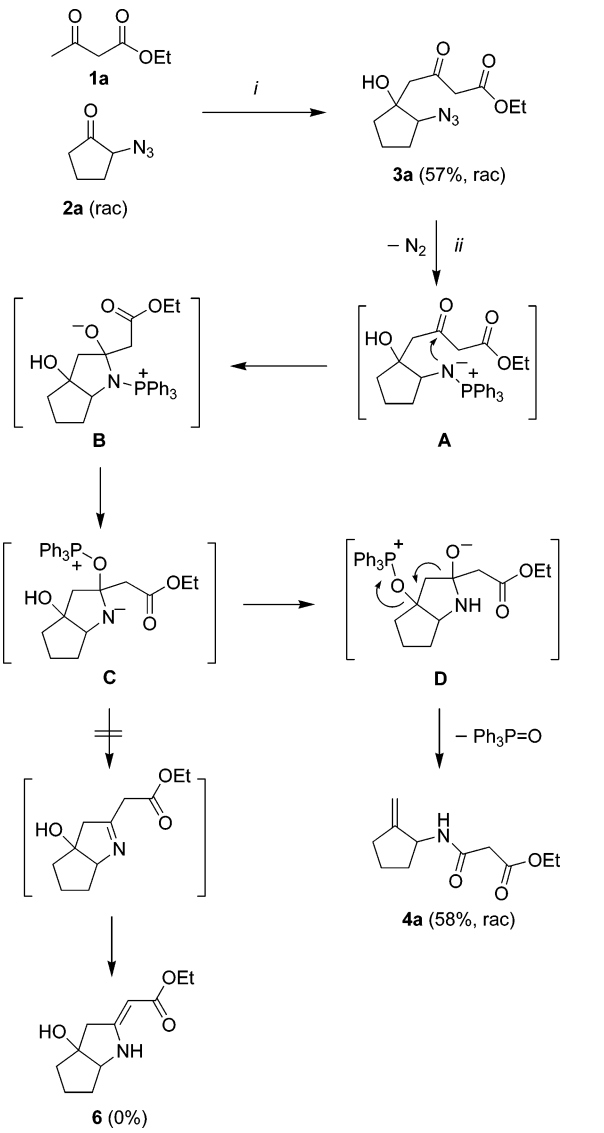
dianions,[13] we recently discovered an unprecedented PPh_3 mediated transformation of γ-azido-β-hydroxyketones.[14] The reaction of PPh_3 with 2-azido-1-hydroxy-1-(2,4-dioxoalkyl)-cyclopentanes, readily available by condensation of 1,3-dicarbonyl dianions with 2-azidocyclopentanone, afforded 1-(1,3-dioxoalkyl)amino-2-(alkylidene)cyclopentanes by means of a domino "Staudinger/semi-aza-Wittig/fragmentation" reaction. Herein, we wish to report full details of these reactions and studies related to scope and limitations. The products prepared represent versatile synthetic building blocks and are of pharmacological relevance.[15]

Results and Discussion

Mechanism. The reaction of the dianion[16] of ethyl acetoacetate (**1a**) with α-azidocyclopentanone (**2a**) afforded 2-azido-1-hydroxy-1-(4-ethoxy-2,4-dioxobutyl)cyclopentane (**3a**), which was formed with very good 1,2-diastereoselectivity (ds > 98:2). The configuration of the product could not be unambiguously assigned. Detailed NMR studies were carried out on a sample of derivative **3q** (vide infra) containing a small amount of the minor isomer. NOESY experiments gave ambigious results (NOE's between the hydrogen atoms C*H*N_3 and $C_{ring}CH_2$(C═O) were observed for *both* isomers). The signal of hydrogen atom C*H*N_3 is significantly shifted lowfield for the minor compared to the major diastereomer. This lowfield shift might be explained by the fact that the hydrogen atom C*H*N_3 of the cis-diastereomer (minor isomer) is located within the anisotropic cone of the carbonyl group $C_{ring}CH_2$(*C*═*O*). In fact, this effect is not to be expected for the trans-diastereomer (by steric reasons). Additions of nucleophiles to the carbonyl group of 2-azidocyclopentan-1-ones have, to the best of our knowledge, not yet been reported. However, a number of reactions of enolates with 2-substituted cyclopentanones are known. In most of these reactions, the *cis*-configured diastereomers were predominantly formed.[17]

Treatment of **3a** with PPh_3 afforded the 1-(1,3-dioxoalkyl)-amino-2-(methylidene)cyclopentane **4a** in up to 58% yield (Scheme 1). The formation of **4a** can be explained by Staudinger reaction of the azide with PPh_3 to give the iminophosphorane **A**, attack of the nitrogen atom of **A** onto the carbonyl group (intermediate **B**), shift of the phosphonium moiety (intermediate **C**), and fragmentation (intermediate **D**) with extrusion of triphenylphosphine oxide. The overall process can be regarded as a domino[18] Staudinger/semi-sza-Wittig/fragmentation reaction. A normal aza-Wittig reaction (leading to **6**) was *not* observed.

SCHEME 1. Proposed Mechanism of the Formation of 4a[a]



[a] (*i*) 2.6 equiv LDA, THF, 0 °C, then **1a** (1.1 equiv), 15 min, then **2a** (1.0 equiv), −78 → 20 °C within 12 h, then 3 h at 20 °C; (*ii*) PPh_3, THF, 24 h, 45 °C.

The reaction time (16 h), stoichiometry and temperature (45 °C) proved to be important parameters during the optimization. The use of PPh_3 (or $P(n\text{Bu})_3$ which was equally successful)[19] proved to be mandatory. Notably, the hydrogenation of **3a** (H_2, cat. Pd/C) afforded the pyrrolidine **6**, albeit in low yield, by reduction of the azide to an amino group and subsequent attack of the latter onto the carbonyl group (Scheme 2).

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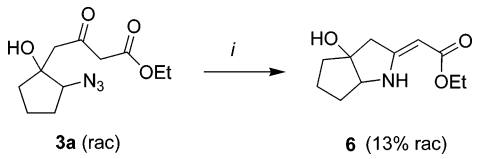
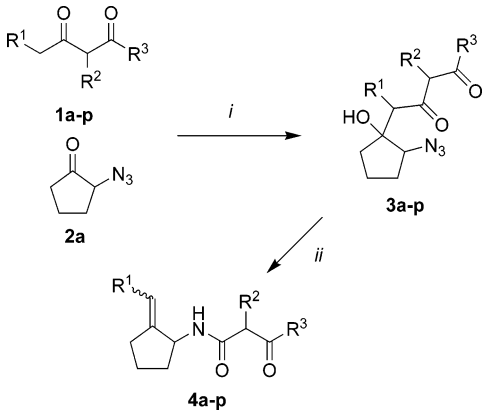
SCHEME 2. Hydrogenation of 3a[a]



3a (rac) **6** (13% rac)

[a] (*i*) H_2, Pd/C.

SCHEME 3. Synthesis of 4a−p[a]

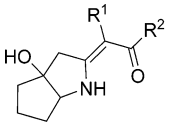


[a] (*i*) 2.6 equiv LDA, THF, 0 °C, then **1a**−**p** (1.1 equiv), 15 min, then **2a** (1.0 equiv), −78 → 20 °C within 12 h, then 3 h, 20 °C; (*ii*) PPh_3, THF, 24 h, 45 °C.

TABLE 1. Products and Yields

3, 4	R^1	R^2	R^3	% (3)[a]	dr[b]	% (4)[a]
a	H	H	OEt	57	> 98:2	58
b	H	H	OMe	55	> 98:2	61
c	H	H	OCH_2Ph	35	10:1	52
d	H	H	$O(CH_2)_2OMe$	64	10:1	61[c]
e	H	H	O*i*Bu	82	10:1	55[g]
f	Me	H	OMe	33	> 98:2[f]	57[d]
g	Et	H	OEt	65	> 98:2[f]	47[d]
h	OMe	H	OMe	54	> 98:2[f]	57[d]
i	H	Me	OEt	40	> 98:2	58[e]
j	H	CH_2Ph	OEt	32	> 98:2	50[e,g]
k	H	Et	OEt	41	> 98:2	49[e]
l	H	*n*Bu	OEt	45	> 98:2	51[e,g]
m	H	H	Me	48	10:1	37[c]
n	H	H	*t*Bu	38	2:1	41
o	Me	H	Et	25	> 98:2[f]	38
p	H	H	Ph	15	10:1	45

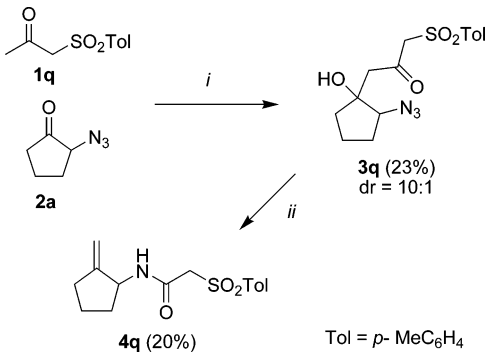
[a] Yields of isolated products. For a number of products **3**, impurities (by partial decomposition) could not be completely removed. [b] The diastereomeric ratio refers to the relative configuration of alcohol and azido group. [c] Triphenylphosphine oxide could not be separated. [d] Configuration of the exocyclic double bond: **4g**−**h**: *E*/*Z* = 3:1; **4f**,**o**: *E*/*Z* = 2:1. [e] dr = 2:1−1:1 (assignment arbitrary). [f] Two diastereomers (3:1−1:1) with respect to the relation of the OH and R^1 groups. [g] Besides, **4e′**, **4j′**, and **4l′** (structures see below) were isolated.



4e' (R^1 = H, R^2 = O*i*Bu), 11%
4j' (R^1 = Bn, R^2 = OEt), 17%
4l' (R^1 = *n*Bu, R^2 = OEt), 19%

Scope and Limitations. The reactions of α-azidocyclopentanone (**2a**) with various 1,3-dicarbonyl dianions were next studied (Scheme 3, Table 1). The condensation of **2a** with the dianions of methyl, benzyl, methoxyethyl, and *iso*-butyl acetoacetate (**1b**−**e**) gave the 2-azido-1-hydroxy-1-(2,4-dioxoalkyl)cyclopentanes **3b**−**e**. Treatment of **3b**−**e** with PPh_3 afforded the 1-(4-alkoxy-2,4-dioxobutyl)amino-2-(methylidene)cyclopentanes **4b**−**e**. The 2-azido-1-hydroxycyclopentanes **3f**−**h** were prepared by reaction of **2a** with the dianions of methyl 3-oxopentanoate (**1f**), ethyl 3-oxohexanoate (**1g**), and methyl 4-methoxyacetoacetate (**1h**) which all contain an additional substituent (R^1 = Me, Et, MeO) located at carbon atom C-4 of the β-ketoester. Treatment of **3f**−**h** with PPh_3 furnished the 1-amino-2-(alkylidene)cyclopentanes **4f**−**h** containing the additional substituent R^1 located at the exocyclic double bond. The products were isolated as unseparable mixtures of *E*/*Z* isomers. The condensation of **2a** with ethyl 2-methyl-, ethyl 2-benzyl-, ethyl 2-ethyl-, and ethyl 2-butylacetoaetate (**1i**−**l**)—all containing a substituent located at carbon atom C-2 of the β-ketoester—gave the 2-azido-1-hydroxycyclopentanes **3i**−**l**. The reaction of the latter with PPh_3 afforded the 1-amino-2-(methylidene)cyclopentanes **4i**−**l**. The employment of 1,3-diketones rather than β-ketoesters was next studied. The condensation of the dianions of pentane-2,4-dione (**1m**), 5,5-dimethylhexane-2,4-dione (**1n**), heptane-3,5-dione (**1o**), and benzoylacetone (**1p**) gave **3m**−**p**. Treatment of **3m**−**p** with PPh_3 furnished the 1-(2,4-dioxoalkyl)amino-2-(alkylidene)cyclopentanes **4m**−**p**. Azido alcohols **3a**−**p** were formed with good to very good *trans*-1,2-diastereoselectivity (except for **3n**). The pyrrolidines **4e′**, **4j′**, and **4l′** were isolated in low yield as side products.

SCHEME 4. Synthesis of 4q[a]



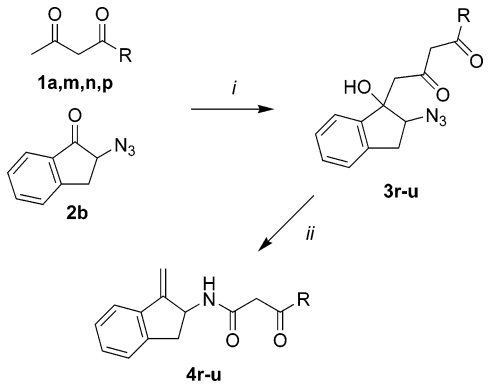
[a] (*i*) (1) 2.6 equiv. LDA, THF, 0 °C, 20 min; (2) **1q** (1.1 equiv), 1 h, then **2a** (1.0 equiv), −78 → 20 °C, 21 h; (*ii*) PPh_3, THF, 38 h, 45 °C.

The condensation of α-azidocyclopentanone (**2a**) with the dianion of tosylacetone afforded 2-azido-1-hydroxy-1-(3-tosyl-2-oxopropyl)cyclopentane (**3q**) with good diastereoselectivity. Treatment of the latter with PPh_3 furnished the 1-amino-2-(methylidene)cyclopentane **4q** (Scheme 4). Despite the low yield, side-products could not be isolated.

The reaction of the dianion of ethyl acetoacetate with 2-azidoindan-1-one (**2b**) afforded the 2-azido-1-hydroxyindane **3r** with good diastereoselectivity (Scheme 5, Table 2). The assignment of the relative configuration remains unclear at present. Treatment of **3r** with PPh_3 resulted in formation of the 2-amino-1-(methylidene)indane **4r** (as an unseparable 4:1 mixture with pyrrolidine **4r′**). The reaction of the dianions of pentane-2,4-dione (**1m**), 5,5-dimethylhexane-2,4-dione (**1n**), and benzoylacetone (**1p**) gave **3s**−**u**. The latter were transformed into the 2-amino-1-(methylidene)indanes **4s**−**u** (**4t** was isolated as an unseparable 1:1 mixture with pyrrolidine **4t′**).

The reaction of 1,3-dicarbonyl dianions with open-chained azides was next studied. The condensation of the dianion of acetylacetone with α-azidoacetone (**2c**) afforded **3v** which was successfully transformed into **4v** (Scheme 6, Table 3). The azido alcohol **3w** was prepared by reaction of 2-azidobutan-3-one (**2d**)

SCHEME 5. Synthesis of 4r−u[a]

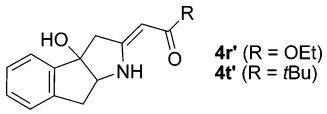


[a] (*i*) 2.6 equiv LDA, THF, 0 °C, then **1a**,**m**,**n**,**p** (1.1 equiv), 15 min, then **2b** (1.0 equiv), −78 → 20 °C within 12 h, then 3 h, 20 °C; (*ii*) PPh_3, THF, 24 h, 45 °C.

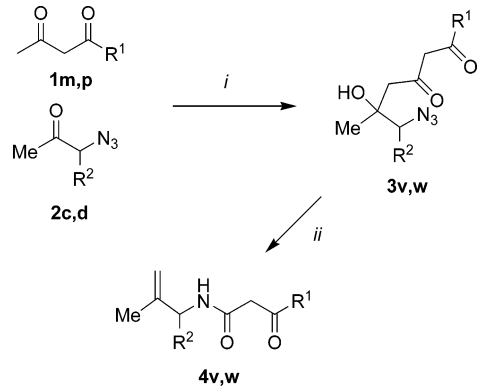
TABLE 2. Products and Yields

3,**4**	R	% (**3**)[a]	dr[b]	% (**4**)[a]
r	OEt	63	10:1	35[c]
s	Me	54	2:1	52
t	*t*Bu	61	5:1	50[d]
u	Ph	55	5:1	46

[a] Yields of isolated products. For a number of products **3**, impurities (by partial decomposition) could not be completely removed. [b] Diastereomeric ratio (assignment arbitrary). [c] Unseparable mixture **4r**/**4r′** = 4:1. [d] Unseparable mixture **4t**/**4t′** = 1:1.



SCHEME 6. Synthesis of 4v,w[a]



[a] (*i*) 2.6 equiv LDA, THF, 0 °C, then **1m**,**p** (1.1 equiv), 15 min, then **2c**,**d** (1.0 equiv), −78 → 20 °C within 12 h, then 3 h, 20 °C; (*ii*) PPh_3, THF, 24 h, 45 °C.

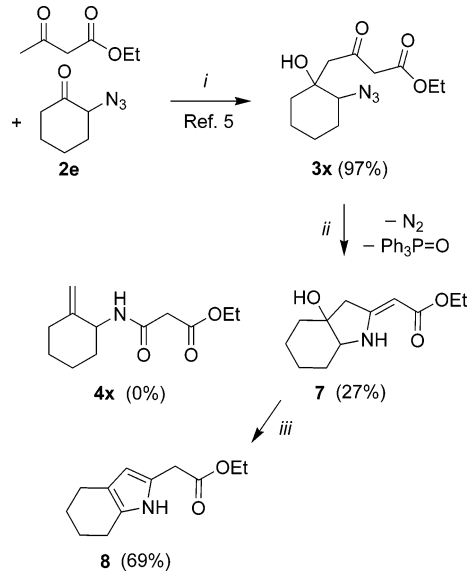
TABLE 3. Products and Yields

3, **4**	R^1	R^2	% (**3**)[a]	% (**4**)[a]	% (**5**)[a]	% (**6**)[a]
v	Me	H	60	30	0	0
w	Ph	Me	52	63	0	15

[a] Yields of isolated products. All azido alcohols **3** were obtained as diastereomeric mixtures (dr = 3:1−1:1, assignment arbitrary).

with the dianion of benzoylacetone. Treatment of **3w** with PPh_3 afforded **4w**. A successful domino reaction of open-chained 1,2-azido alcohols required the use of 1,3-diketones. In contrast, the formation of pyrroles was observed for open-chained 1,2-azido alcohols derived from *β-ketoesters*.[5] The reason for this different behavior remains unclear at present. Notably, we have reported earlier[7] that the reaction of PPh_3 with $N_3CH_2CH(OMe)CH_2(CO)CH_2(CO)CH_3$, containing a capped (albeit secondary rather than tertiary) hydroxy group, resulted in the formation of a 2-alkylidenepyrrolidine rather than rearrangement. This result supports the assumption (vide supra) that the presence of a free hydroxy group is necessary for the rearrangement to occur.

SCHEME 7. Reaction of PPh_3 with 2-Azido-1-hydroxycyclohexane 3x (ref 5)[a]



[a] (*i*) (1) 2.4 equiv. LDA, THF, 0 °C; (2) −78 → 20 °C; (*ii*) PPh_3, CH_2Cl_2, 24 h, THF, 45 °C; (*iii*) TFA, CH_2Cl_2, 1 h, 20 °C.

We have reported earlier that the condensation of the dianion of ethyl acetoacetate with 2-azidocyclohexanone (**2e**) afforded the 2-azido-1-hydroxycyclohexane **3x** (Scheme 7).[5,20] The reaction of **3x** with PPh_3 furnished the bicyclic 2-alkylidenepyrrolidine **7** (which was subsequently transformed into the tetrahydroindole **8**).[5,20] The formation of 1-amino-2-(alkylidene)-cyclohexane **4x** was *not* observed. The formation of pyrrolidines rather than 1-amino-2-(alkylidene)cycloalkanes was observed also for 7-, 8- and 12-membered rings.[5,20] The normal aza-Wittig reaction of six-membered ring **3x** proceeds by initial formation of a bicyclic imine which undergoes a 1,3-H shift to give **7**. The normal aza-Wittig reaction of **3a** would result in the formation of the more strained 5,5-bicyclic product **6** (see Scheme 2) which seems to be less stable than the corresponding 5,6-bicyclic product **7**. Notably, the ring-size of the starting material influences the competition between the normal aza-Wittig and the domino Staudinger/semi-aza-Wittig/fragmentation reaction.

The LDA mediated reaction of acetone with **2a** failed. In contrast, the $TiCl_4$ mediated reaction of 2-(trimethylsilyloxy)-prop-2-ene with **2a** (Mukaiyama aldol reaction) afforded **3y** in good yield (Scheme 8). Treatment of **3y** with PPh_3 afforded the known[21] 5,5-bicyclic pyrrole **9** rather than the expected 1-amino-2-(methylidene)cyclopentane **4y**. This experiment shows that the presence of a 1,3-dicarbonyl or related subunit (see **4q**) represents an important structural feature of the starting material for a domino reaction to be observed.

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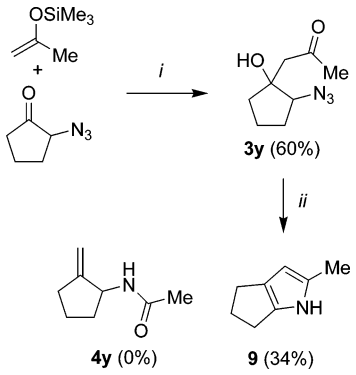
SCHEME 8. Reaction of 3y with PPh_3[a]



[a] (*i*) (1) $TiCl_4$, CH_2Cl_2, 0 °C; (2) −78 → 20 °C; (*ii*) PPh_3, 24 h, THF, 45 °C.

Conclusions. The competition between the domino Staudinger/semi-aza-Wittig/fragmentation reaction and the normal aza-Wittig reaction is influenced by a number of parameters. The presence of a γ-azido-β-hydroxyketone moiety is the minimal structural requirement for a domino reaction to be observed. It was shown that the domino process is most likely to be observed when a cyclopentane derivative, that is, a 2-azido-1-hydroxy-1-(2,4-dioxoalkyl)cyclopentane, is employed. The use of an acceptor-substituted ketone, for example, a 1,3-diketone, a β-ketoester, or a β-ketosulfone is required. For open-chained γ-azido-β-hydroxyketones, the domino process is only observed for 1,3-diketones.

Experimental Section

General. All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectrometric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60−200 mesh) was used. Melting points are uncorrected. The α-azidoketones **2a**−**f** were prepared according to literature procedures. 2-Azidocyclopentanone (**2f**) was prepared from 2-chlorocyclopentanone.[22] 2-Azidoindan-1-one (**2b**) was prepared in three steps by a literature procedure.[23] 1-Azidopropan-2-one (**2c**) was prepared from 3-chlorobutan-2-one and NaN_3.[24] 3-Azidobutan-2-one (**2d**) was prepared by the reaction of 3-chlorobutan-2-one with NaN_3.[25] 2-Azidocyclohexanone (**2e**) was prepared from 2-chlorocyclohexanone.[26]

CAUTION: The handling of azides is dangerous, because of their potentially explosive character. Although, in our hands, azides **2** did not appear to be shock sensitive, the compounds should be handled with great care. Neat azides must not be heated or distilled and all reactions should be carried out on a small scale. The use of a safety shield is highly recommended.

General Procedure for the Synthesis of 2-Azido-1-hydroxy-1-(2,4-dioxoalkyl)cyclopentanes 3a−w. To a solution of diisopropylamine (2.6 equiv) in anhydrous THF (35 mL) was added *n*BuLi (2.6 equiv, 23% or 15% solution in hexanes) at 0 °C. After stirring for 15 min the dicarbonyl compound **1** (1.1 equiv) was added, and the solution was stirred for 1 h at 0 °C. A THF solution (5 mL) of azidoketone **2** (1.0 equiv) was added at −78 °C, and the reaction mixture was warmed to ambient temperature during 12 h. After stirring for further 3 h at 20 °C, a saturated aqueous solution of NH_4Cl (50 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 70 mL) and with CH_2Cl_2 (2 × 50 mL). The combined organic layers were extracted with brine, dried (Na_2SO_4), and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:4 → 1:3) to give the alcohol **3**. Because of its instability, the product should be used for further transformations within 24 h. In some cases, small amounts of decomposition products could not be removed. The following products reside in their enolic form: **3n**−**u**,**w**−**y**.

Ethyl 4-(2-Azido-1-hydroxycyclopentyl)-3-oxobutyrate (3a). The starting materials diisopropylamine (0.63 g, 6.30 mmol), *n*BuLi (4.1 mL, 6.30 mmol, 15% solution in hexane), ethyl acetoacetate (**1a**) (0.34 g, 2.64 mmol), and 2-azidocyclopentanone (**2a**) (0.30 g, 2.40 mmol) yielded **3a** as a yellow oil (0.51 g, 57%, dr > 98:2). ^1H NMR (300 MHz, $CDCl_3$, major isomer): δ = 1.25 (t, ^3J = 7 Hz, 3 H), 1.55−2.04 (m, 6 H), 2.63 (d, ^2J = 16 Hz, 1 H), 2.98 (d, ^2J = 16 Hz, 1 H), 3.32 (t, ^3J = 6 Hz, 1 H), 3.45 (s, 2 H), 4.18 (q, ^3J = 7 Hz, 2 H). ^{13}C NMR (50.3 MHz, $CDCl_3$, major isomer): δ = 14.0, 19.2, 26.9, 36.0, 49.8, 50.4, 61.5, 67.7, 79.8, 166.9, 203.3. IR (neat): $\tilde{\nu}$= 3503 (br, w), 2978 (w), 2106 (d), 1740 (s), 1711 (s), 1446 (w), 1407 (w), 1369 (w), 1318 (m), 1258 (m), 1181 (m), 1096 (w), 1028 (m) cm^{-1}. MS (DCI, NH_3): *m*/*z* (%) = 528 ([2M + NH_4]$^+$, 84), 483 (80), 438 (22), 273 ([M + NH_4]$^+$, 100), 228 (36), 210 (18). Anal. Calcd for $C_{11}H_{17}N_3O_4$ (255.27): C, 51.70; H, 6.66. Found: C, 51.59; H, 6.43.

3-(2-Azido-1-hydroxycyclopentyl)-1-tosylpropan-2-one (3q). To a THF solution (100 mL) of diisopropylamine (3.68 g, 36.4 mmol) was added a 1.6 M solution of *n*BuLi in hexane (22.8 mL, 36.5 mmol) at 0 °C. After the mixture was stirred for 20 min, 1-tosylpropan-2-one (2.89 g, 13.6 mmol) was added, and the solution was stirred for 1 h at 0 °C. 2-Azidocyclopentanone (1.70 g, 13.6 mmol) was added at −78 °C, and the reaction mixture was warmed to ambient temperature within 21 h. A saturated solution of NH_4Cl (100 mL) was added, and the organic layer was separated. The organic layer was extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, hexane/ethyl acetate = 3/1) to give **3q** as a brownish oil (1.06 g, 23%, dr = 10:1). An analytical sample of the pure cis-diastereomer could be separated. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.50−1.75 (m, 2 H), 1.75−2.10 (m, 4 H), 2.46 (s, 3 H), 2.83 (d, ^2J = 16.4 Hz, 1 H), 3.14 (d, ^2J = 16.4 Hz, 1 H), 3.37 (dd, $^3J_1$ = $^3J_2$ = 8.4 Hz, 1 H), 4.17 (d, ^2J = 13.1 Hz, 1 H), 4.31 (d, ^2J = 13.1 Hz, 1 H), 7.38 (d, ^3J = 8.2 Hz, 2 H), 7.76 (d, ^3J = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.2, 21.6, 27.0, 35.9, 51.4, 67.7, 68.0, 79.8, 128.2, 130.0, 135.5, 145.6, 198.5.

General Procedure for the Synthesis of 1-Amino-2-(alkylidene)cyclopentanes 4a−w. To a anhydrous THF solution (15 mL) of **3** was added PPh_3 (1.2 equiv) at 20 °C, and the reaction mixture was stirred for 24 h at 45 °C. The solution was cooled to ambient temperature, and water (80 mL) was added. The organic and the aqueous layer were separated, and the latter was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were extracted with brine (1 × 80 mL), dried (Na_2SO_4), and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, ether/petroleum ether = 1:2 or ether/petroleum ether = 1:40 → 1:3) to give compounds **4**.

***N*-(2-Methylenecyclopentyl)malonamic Acid Ethyl Ester (4a).** Treatment of **3a** (0.39 g, 1.55 mmol) with PPh_3 yielded, after purification by chromatography (silica gel, ether/petroleum ether = 1:40 → 1:3), **4a** as a yellow solid (0.19 g, 58%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7 Hz, 3 H), 1.38 (m, 1 H), 1.62 (m, 1 H), 1.73 (m, 1 H), 2.16 (m, 1 H), 2.37 (m, 2 H), 3.31 (s, 2 H), 4.17 (q, ^3J = 7 Hz, 2 H), 4.62 (dd, ^3J = 7 Hz, ^3J = 3 Hz, 1 H), 4.98 (m, 2 H), 7.05 (br, 1 H). ^{13}C NMR (50.3 MHz, $CDCl_3$): δ =

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14.0, 22.3, 30.9, 33.8, 41.2, 53.7, 61.5, 106.8, 152.0, 164.7, 169.57. IR (neat) $\tilde{\nu}$ = 3286 (br, m), 2960 (s), 1750 (s), 1650 (s), 1547 (s), 1465 (w), 1417 (w), 1369 (m), 1182 (s), 1033 (m), 885 (w) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 211 (M^+, 65), 123 (18), 97 (56), 96 (100), 81 (28), 69 (29). The exact molecular mass *m*/*z* = 211.1208 ± 2 ppm [M^+] for $C_{11}H_{17}NO_3$ was confirmed by HRMS (EI, 70 eV).

***N*-(2-Methylidenecyclopentyl)-2-tosylacetamide (4q).** Compound **3q** (260 mg, 0.77 mmol) was dissolved in dry THF (10 mL), and triphenylphosphine (244 mg, 0.93 mmol) was added. The reaction mixture was stirred at 45 °C for 38 h. Water (50 mL) and CH_2Cl_2 (50 mL) were added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by chromatography (silica gel, petroleum ether/ethyl acetate = 3/1) to give **4q** as a yellow solid (46 mg, 20%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.37−1.52 (m, 1 H), 1.52−1.71 (m, 1 H), 1.71−1.85 (m, 1 H), 2.07−2.20 (m, 1 H), 2.36−2.44 (m, 2 H), 2.45 (s, 3 H), 4.02 (d, ^2J = 1.1 Hz, 2 H), 4.58 (m, br, 1 H), 5.03 (m, 2 H), 6.67 (d, br, ^3J = 7.3 Hz, 1 H), 7.37 (d, ^3J = 8.2 Hz, 2 H), 7.79 (d, ^3J = 8.2 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 21.7, 22.4, 30.9, 33.6, 54.1, 62.0, 107.5, 128.1, 130.0, 135.2, 145.6, 151.3, 160.3. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3331 (s), 2993 (m), 2964 (m), 2917 (m), 1650 (s), 1521 (s), 1324 (s), 1299 (m), 1159 (s), 1087 (m), 814 (m), 522 (m). MS (EI, 70 eV): *m*/*z* (%) = 294.0 ([M + 1]$^+$, 2), 293.0 (M^+, 20), 214.0 (4), 155.1 (6), 138.1 (100), 96.1 (30), 91.0 (36), 32.1 (23), 28.1 (90). HRMS (EI, 70 eV): calcd for $C_{15}H_{19}NO_3S$ (M^+), 293.10802; found, 293.10758.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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