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A method for synthesis of bicyclo[3.3.0]oct-1-en-3-ones from cyclobutanones with one-carbon ring expansion and its application to a formal synthesis of racemic 1-desoxyhypnophilin

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Abstract—A method for synthesis of 2-cyanobicyclo[3.3.0]oct-1-en-3-ones and 2-substituted bicyclo[3.3.0]oct-1-en-3-ones was developed by assembly of three components, cyclobutanones, chloromethyl *p*-tolyl sulfoxide, and nitriles, with one-carbon ring expansion of the cyclobutane ring. As an application of this method, a formal synthesis of 1-desoxyhypnophilin in racemic form was performed starting from 3,3-di(phenylthiomethyl)cyclobutanone.

1. Introduction

To date, numerous natural products containing fused five-membered rings have been isolated and they are called polyquinane natural products. The natural products containing three five-membered rings are triquinanes and they are classified into two categories, linear triquinanes and angular triquinanes.[1] Both triquinanes contain a bicyclo[3.3.0]octane ring as the basic skeletal structure. The unique structure and promising biological activities of triquinanes have stimulated biochemists and organic chemists for a long time, and enormous efforts were made for the chemical synthesis of these compounds.[2]

As for the synthesis of the bicyclo[3.3.0]octane ring system, various kinds of methods have appeared including aldol-type annulation,[3] Nazarov cyclization,[4] and Pauson–Khand reaction.[5] Especially, asymmetric Pauson–Khand reaction is recognized to be quite promising for the synthesis of optically active natural products.[6] On the other hand, a few methods for the construction of a fused five-membered ring by ring expansion of cyclobutane derivatives have been reported.[7] We have also been interested in the ring-expansion reactions.[8]

Recently, we reported a new method for synthesis of spiro-type 2-cyclopentenones from cyclic ketones through 1-chlorovinyl *p*-tolyl sulfoxides with nitriles.[9] In continuation of our investigation of this chemistry we found that when cyclobutanones were used as the cyclic ketones in this procedure, bicyclo[3.3.0]oct-1-en-3-ones could be synthesized.[10] In this paper we describe, in detail, this chemistry and an application of this methodology to a formal synthesis of racemic 1-desoxyhypnophilin.

The essence of the chemistry described hereafter is as follows (Scheme 1). Thus, 1-chlorovinyl *p*-tolyl sulfoxides **1** are synthesized starting from cyclobutanones and chloromethyl *p*-tolyl sulfoxide in three steps in high overall yields. Reaction of vinyl sulfoxides **1** with excess cyanomethyllithium results in spiro-type enaminonitrile **2**. Treatment of **2** with acid under heating gives 2-cyanobicyclo[3.3.0]oct-1-en-3-one **3**. On the other hand, treatment of the vinyl sulfoxides **1** with cyanomethyllithium followed by lithium α-carbanion of nitriles affords enaminonitriles **4**. Heating of **4** with acid gives 2-substituted bicyclo[3.3.0]oct-1-en-3-ones **5** in good yields. By using this method, linear triquinane **7**, an intermediate for the total synthesis of 1-desoxyhypnophilin, is synthesized starting from 3,3-di(phenylthiomethyl)cyclobutanone **6** in good yield.

2. Results and discussion

2.1. Synthesis of 2-cyanobicyclo[3.3.0]oct-1-en-3-one from cyclobutanone and its reactions

First, [chloro(*p*-tolylsulfinyl)methylidene]cyclobutane **8** was synthesized starting from cyclobutanone and

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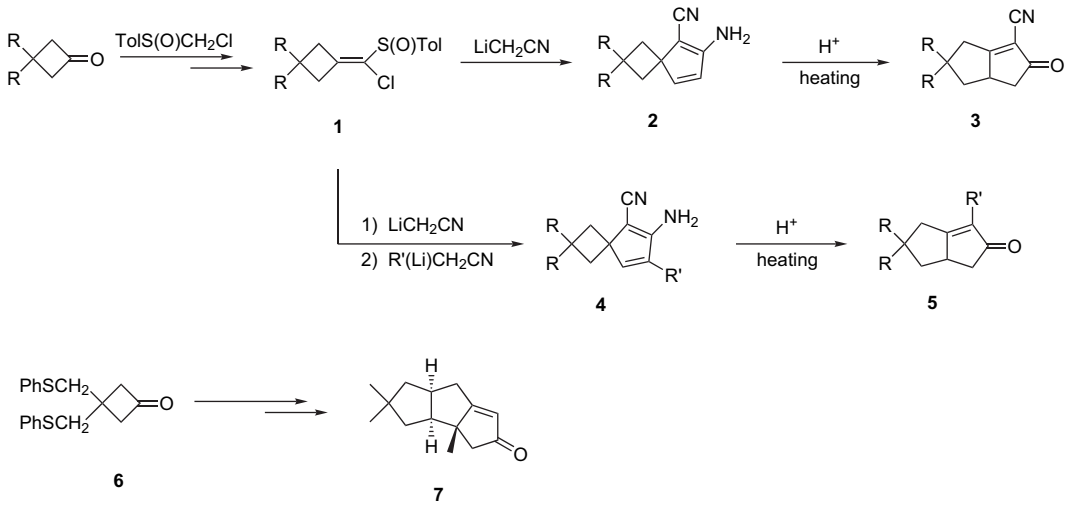
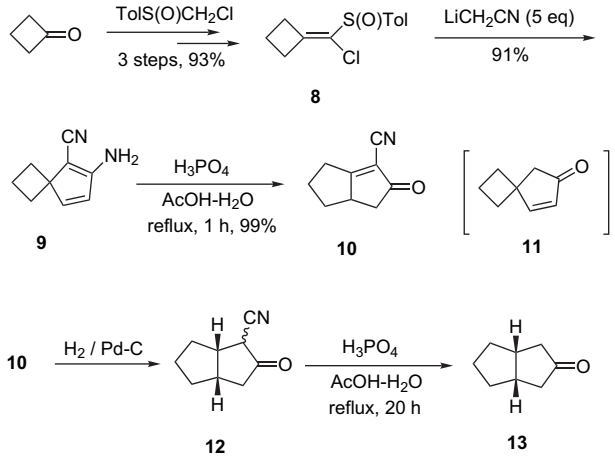


Scheme 1.

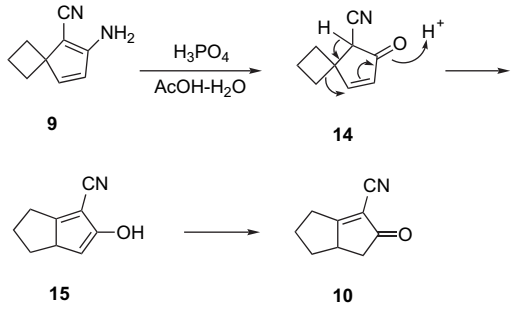
chloromethyl *p*-tolyl sulfoxide in three steps in 93% overall yield.[9] Vinyl sulfoxide **8** was treated with 5 equiv of cyanomethyllithium in THF to give the expected enaminonitrile **9** in 91% yield.[9] Finally, enaminonitrile **9** was heated with H_3PO_4 in acetic acid containing water for 1 h to give a clean reaction mixture from which a cyclopentenone derivative was obtained in quantitative yield (Scheme 2).



Scheme 2.

Initially, we anticipated that the product would be spiro[3.4]alkenone **11** on the basis of our experience.[9] However, the product has a cyano group and the structure of the product **10** was presumed to be 2-cyanobicyclo[3.3.0]oct-1-en-3-one judging from ^1H and ^{13}C NMR. In order to confirm the skeletal structure of **10**, the product was hydrogenated to ketone **12** followed by hydrolysis and decarboxylation to give a known cyclopentanone derivative **13**. Spectral data for the product **13** were found to be in agreement with those reported for bicyclo[3.3.0]octan-3-one **13**.[11]

A plausible mechanism for the formation of **10** from enaminonitrile **9** by the acid treatment is shown in Scheme 3. Thus, acidic hydrolysis of the enamine function of **9** gives enone **14**. Protonation of the carbonyl oxygen of enone **14** followed by rearrangement of a bond of the cyclobutane ring would give bicyclo[3.3.0]octenol **15**. Tautomerization of the enol portion of **15** finally gives **10**. The simple acid treatment of **9** created bicyclo[3.3.0]octane derivative **10** and it is thought that the strained four-membered ring eventually provides the driving force for the skeletal rearrangement.

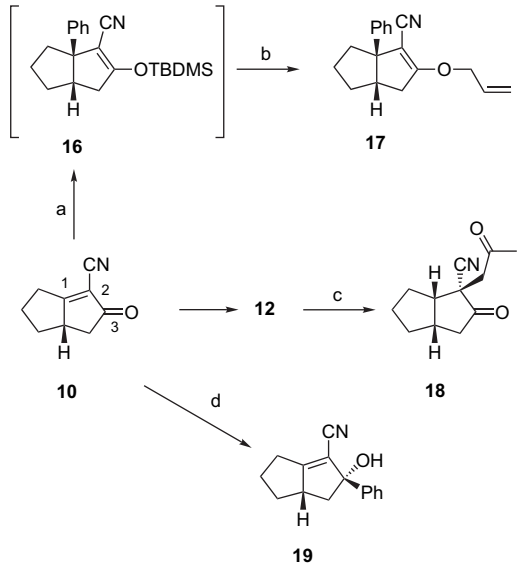


Scheme 3. A plausible mechanism for the formation of **10** from enaminonitrile **9** by the acid treatment.

The product, 2-cyanobicyclo[3.3.0]oct-1-en-3-one, **10** is a quite interesting compound as starting material for the synthesis of polyquinane natural products. We tried some reactions on carbons 1–3 of **10** and the results are summarized in Scheme 4. Thus, TBDMSO-Tf-promoted conjugate addition of **10** and organocuprate prepared from PhMgBr and copper(I) iodide gave quantitative yield of the corresponding silyl enol ether having a phenyl group at the angular position in **16**.[12] This intermediate was treated with methyllithium followed by allyl iodide to give **17** in 65% overall yield from **10**.

On the other hand, treatment of **12** with bromoacetone in the presence of sodium hydride in THF resulted in the formation of a cyanocyclopentanone derivative bearing a 2-oxopropyl group at the 2-position of **18**, which is a good precursor for synthesis of linear triquinane, in good yield. Treatment of **10** with PhMgBr without a copper catalyst resulted in the formation of 1,2-adduct **19** in good yield.

In order to investigate the generality of this reaction, two cyclobutanone derivatives **21a** and **21b** were synthesized



Scheme 4. Some reactions at carbons 1–3 of **10**. Reagents and yields: (a) PhMgBr, CuI, TBDMSO-Tf; (b) CH_3Li, allyl iodide, THF, 65% from **10**; (c) $BrCH_2COCH_3$, NaH, THF, 79%; (d) PhMgBr, THF, 88%.

from reported cyclobutanol derivative **20**, which was derived starting from benzyl bromide and epichlorohydrin.[13] The results are summarized in Scheme 5. 1-Chlorovinyl *p*-tolyl sulfoxides **22a** and **22b** were obtained from the ketones **21a** and **21b**, respectively, in high overall yields by the same procedure as described above without any problem. Treatment of **22a** and **22b** with 5 equiv of cyanomethyllithium afforded the desired enaminonitriles **23a** and **23b** both in 84% yield. The acidic treatment of the enaminonitriles gave the 7,7-disubstituted 2-cyanobicyclo[3.3.0]oct-1-en-3-ones **24a** and **24b** in 66% and 62% yields, respectively. In the case of the reaction with **23b**, the acetal was hydrolyzed and the produced alcohol was acetylated to give acetate **24b**.

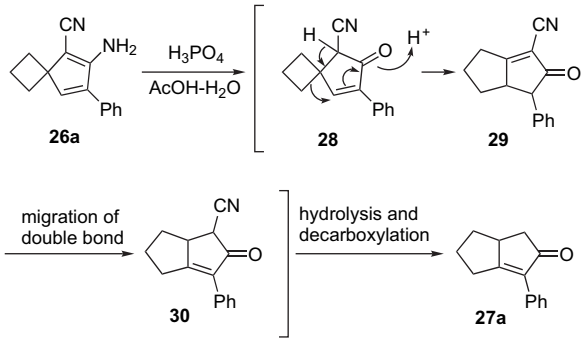
2.2. Synthesis of 2-substituted bicyclo[3.3.0]oct-1-en-3-ones from cyclobutanone

Previously, we reported a novel method for synthesis of 2,4,4-trisubstituted 2-cyclopentenones from 1-chlorovinyl *p*-tolyl sulfoxides by consecutive reaction with cyanomethyllithium and its homologues.[14] This methodology was applied to 1-chlorovinyl *p*-tolyl sulfoxide **8** and very interesting results were obtained as shown in Table 1.

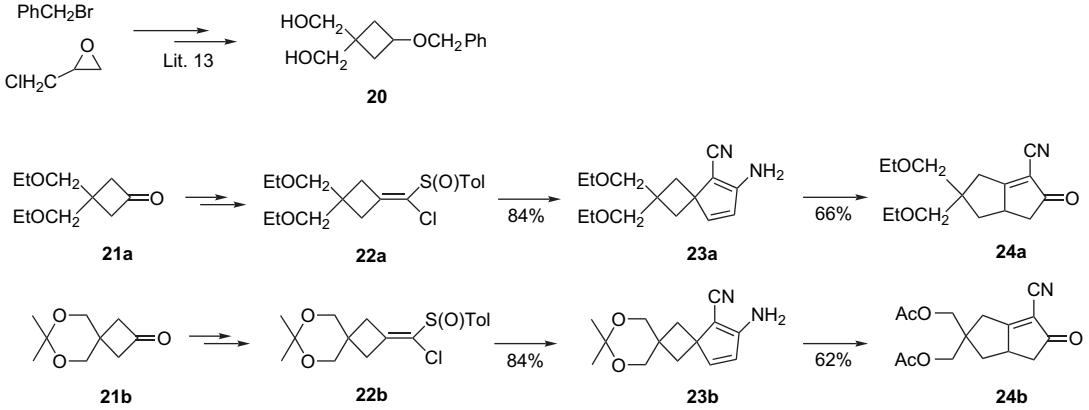
Thus, 1-chlorovinyl *p*-tolyl sulfoxide **8** was treated with 3 equiv of cyanomethyllithium in THF at −78 °C for 10 min to afford adduct **25** in 95% yield. Adduct **25** was then treated with LDA in THF (lithium α-sulfinyl carbanion of **25** was generated) at −78 °C and to this reaction mixture was added slowly a THF solution of 7 equiv of lithium α-carbanion of phenylacetonitrile (entry 1 in Table 1). The reaction mixture was slowly allowed to warm to −40 °C to give the desired enaminonitrile **26a** in 78% yield. Finally, enaminonitrile **26a** was heated under the conditions described above to afford the product in 99% yield.

Quite surprisingly, the obtained compound was not the expected 2-cyano-4-phenylbicyclo[3.3.0]oct-1-en-3-one but 2-phenylbicyclo[3.3.0]oct-1-en-3-one **27a**. Spectral data for the product **27a** were in good agreement with those reported for 2-phenylbicyclo[3.3.0]oct-1-en-3-one.[15]

A plausible mechanism for the formation of **27a** from enaminonitrile **26a** by heating with acid is as follows (Scheme 6). First, the acidic hydrolysis of the enamine portion of **26a** gives enone **28**. The ring expansion of the cyclobutane ring would take place as described above (see Scheme 3) to give 2-cyano-4-phenylbicyclo[3.3.0]oct-1-en-3-one **29**. Migration of the double bond in **29** occurs under the acidic conditions to afford **30**. Finally, the cyano group is hydrolyzed followed by decarboxylation to afford the product **27a**.

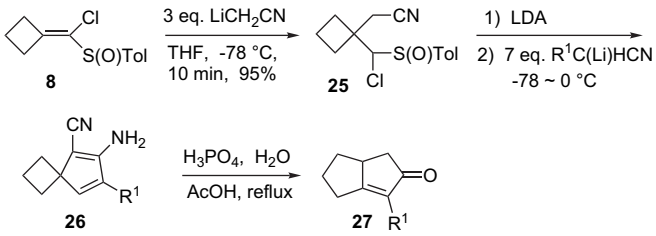


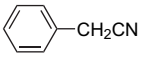
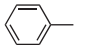
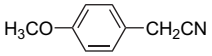
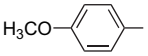
Scheme 6. A plausible mechanism for the formation of **27a** from enaminonitrile **26a** by the acid treatment.



Scheme 5. Synthesis of 2-cyanobicyclo[3.3.0]oct-1-en-3-ones **24a** and **24b** from cyclobutanones **21a** and **21b**.

Table 1. Synthesis of 2-substituted bicyclo[3.3.0]oct-1-en-3-one **27** from vinyl sulfoxide **8** with cyanomethyllithium and its homologues through enaminonitrile **26**



Entry	R^1CH_2CN	Enaminonitrile **26**		Conditions for hydrolysis (h)	2-Substituted bicyclo[3.3.0]oct-1-en-3-one **27**		
			Yield %			R^1	Yield %
1		**26a**	78[a]	12	**27a**		99
2		**26b**	99	14	**27b**		75
3	CH_3CH_2CN	**26c**	97	65	**27c**	CH_3	78
4	$CH_3(CH_2)_3CH_2CN$	**26d**	95	85	**27d**	$CH_3(CH_2)_3$	83
5	Ph_3CCH_2CN	**26e**	64	50	**27e**	Ph_3C	53

[a] Conditions: −78 to −40 °C and −40 °C for 1.5 h.

Because the product **27a** and its congeners are thought to be very important compounds for synthesis of polyquinanes, we investigated the generality of this reaction using a variety of nitriles and the results are summarized in Table 1. The reaction using 4-methoxyphenylacetonitrile also gave the enone having an aryl group at 2-position of **27b** in good overall yield from **25** (entry 2). Entries 3 and 4 show that both the methyl group and the long alkyl group can be introduced at the 2-position of the enone in good overall yields. Interestingly, it was found that the enaminonitriles having alkyl groups need much longer time for the hydrolysis compared with those having aryl groups. A very bulky triphenylmethyl group can be placed at the 2-position by this method though the overall yield was not satisfactory (entry 5).

2.3. A formal synthesis of desoxyhypnophilin

Finally, we applied our above-mentioned method for synthesis of 2-substituted bicyclo[3.3.0]oct-1-en-3-one to a formal total synthesis of desoxyhypnophilin and the results are summarized in Scheme 7. We selected the reported cyclobutanol derivative **20** as the starting material.

At first, both hydroxyl groups of **20** were converted to bissulfide **31** in quantitative yield by the conventional method. The deprotection of the benzyl group of **31** by catalytic hydrogenation using Pd as catalyst did not work at all because of the presence of the sulfur. Fortunately, removal of the benzyl group was effective with TMSI as reported by Jung[16] to afford alcohol **32**; however, the yield was not satisfactory. The hydroxyl group of **32** was oxidized under Swern's conditions to give cyclobutanone **6** in quantitative yield.

Cyclobutanone **6** was converted to 1-chlorovinyl *p*-tolyl sulfoxide **33** in 93% overall yield without any problem in the procedure described above. The addition reaction of cyanomethyllithium to the vinyl sulfoxide **33** proceeded smoothly to give adduct **34** in 94% yield. We encountered some problems in the next step. Treatment of **34** with LDA followed by lithium α-carbanion of propionitrile, the procedure mentioned above, gave rather complex mixture and the desired enaminonitrile **35** was obtained in only 45% yield. This problem was overcome by direct treatment of **34** with excess lithium α-carbanion of propionitrile to give the desired **35** in 91% yield.

The acidic treatment of **35** was found to be sluggish; however, the desired 2-methylbicyclo[3.3.0]oct-1-en-3-one **36** was obtained in 73% yield after 132 h heating. Both the double bond and the sulfide groups were reduced with Raney-Ni in ethanol to give 2,7,7-trimethylbicyclo[3.3.0]-octan-2-one **37** in 77% yield. Allylation of **37** was performed with allyl iodide in THF using NaH as a base[17] to afford **38** as a single isomer in 67% yield.

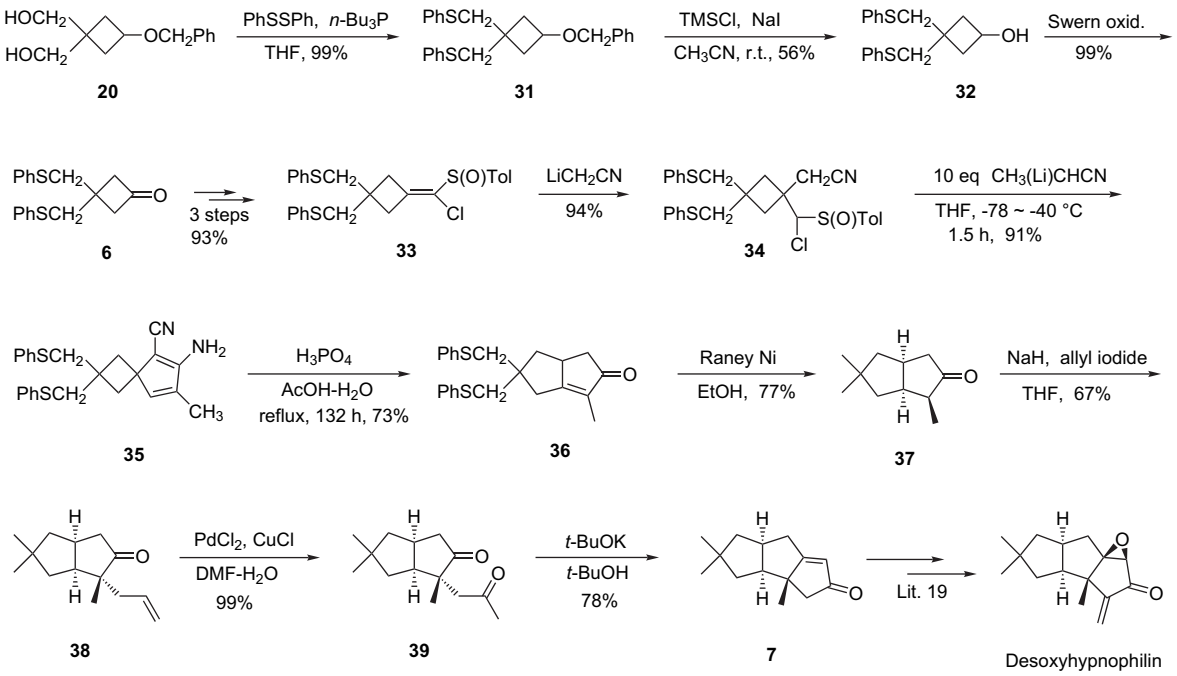
The terminal olefin in **38** was oxidized to a methyl ketone **39** employing Tsuji's procedure.[18] Aldol reaction of the diketone **39** with potassium *tert*-butoxide[19] afforded the desired triquinane **7** in 77% overall yield. All spectral data for the product **7** were highly consistent with those reported for triquinane **7**.[20] Harrowven et al. reported the first total synthesis of racemic 1-desoxyhypnophilin from **7** in two steps.[20]

In conclusion, a new method for synthesis of 2-cyanobicyclo[3.3.0]oct-1-en-3-ones and 2-substituted bicyclo[3.3.0]-oct-1-en-3-ones was established from cyclobutanones with one-carbon ring expansion. The developed method was successfully applied to a formal total synthesis of 1-desoxyhypnophilin.

3. Experimental

3.1. General

All melting points were measured on Yanaco MP-S3 heated stage apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were taken with JEOL JNM A-500 or Bruker DPX 400 and AV 600 spectrometer using $CDCl_3$ solutions with tetramethylsilane as an internal standard. Mass spectra



Scheme 7. A formal synthesis of racemic desoxyhypnophilin from 3,3-di(phenylthiomethyl)cyclobutanone **6** via triquinane **7**.

were measured on a Hitachi M-80 spectrometer. IR spectra were recorded on Spectrum One series Fourier transform infrared spectrometer using either NaCl plates or KBr pellets. Column chromatography was performed with silica gel (Kanto Chemical). In experiments requiring dry reagents and solvents, THF was distilled from sodium-benzophenone ketyl. Diisopropylamine and CH_2Cl_2 were distilled from CaH_2. Acetone was dried over $CaSO_4$ and distilled before use. All reactions involving air- or water-sensitive compounds were routinely conducted in glassware, which was flame-dried under a positive pressure of argon.

3.1.1. [Chloro(*p*-tolylsulfinyl)methylidene]cyclobutane (8). A solution of chloromethyl *p*-tolyl sulfoxide (3.19 g; 16.9 mmol) in dry THF (3 mL) was added dropwise to a solution of LDA (16.9 mmol) in 25 mL of THF at −78 °C. The solution was stirred at −78 °C for 10 min and then cyclobutanone (1.05 mL; 14.1 mmol) was added. The reaction mixture was stirred for 20 min and the reaction was quenched by satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed once with water and dried over $MgSO_4$. The solvent was evaporated to leave the adduct as colorless crystals. The crystals were filtered and used without further purification.

The adduct was dissolved in a mixture of acetic anhydride (27 mL) and pyridine (57 mL). 4-Dimethylaminopyridine (288 mg; 2.35 mmol) was added to the solution and the reaction mixture was stirred at room temperature for 3 h. The acetic anhydride and pyridine were evaporated under vacuum and the residue was purified by silica gel column chromatography to give an acetate (4.0 g; 94%).

To a solution of the acetate (4.0 g; 13.3 mmol) in 8 mL of dry THF was added dropwise with stirring a solution of *N*-lithio-2-piperidone (41.2 mmol), prepared from 2-piperidone and *n*-BuLi in 94 mL of dry THF at 0 °C. After 10 min, the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed once with water. The organic layer was dried over $MgSO_4$ and the product was purified by silica gel flash column chromatography to give **8** (3.17 g; 99%) as colorless crystals; mp 82–83 °C (AcOEt–hexane); IR (KBr) 2966, 2912, 1646, 1493, 1453, 1404, 1086, 1055 (SO), 1016, 882, 810, 529 cm^{-1}; ^1H NMR δ 2.10–2.24 (2H, m), 2.42 (3H, s), 2.80–2.93 (2H, m), 3.09–3.16 (1H, m), 3.21–3.28 (1H, m), 7.32 (2H, d, J=8.0 Hz), 7.50 (2H, d, J=8.0 Hz). MS *m/z* (%) 240 (M^+, 70), 225 (35), 223 (97), 187 (20), 139 (56), 123 (37), 105 (40), 91 (47), 65 (100). Calcd for $C_{12}H_{13}ClOS$: M, 240.0375. Found: *m/z* 240.0383. Anal. Calcd for $C_{12}H_{13}ClOS$: C, 59.87; H, 5.44; Cl, 14.73; S, 13.32%. Found: C, 59.92; H, 5.51; Cl, 14.34; S, 13.27%.

3.1.2. 6-Aminospiro[3.4]octa-5,7-diene-5-carbonitrile (9). Acetonitrile (0.166 mL; 3.18 mmol) was added to a solution of *n*-BuLi (3.12 mmol) in 7.5 mL of dry THF at −78 °C with stirring. The solution was stirred for 10 min and then a solution of **8** (150 mg; 0.623 mmol) in 1.5 mL of dry THF was added dropwise to this solution. The temperature of the reaction mixture was gradually allowed to warm to room temperature over 2 h and the reaction mixture was further stirred at room temperature for 30 min. The reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed once with water. The organic layer was dried over $MgSO_4$ and the product was isolated by silica gel flash column chromatography to give 82.5 mg (91%) of **9** as colorless crystals; mp 63–64 °C (AcOEt–hexane); IR (KBr) 3441, 3349, 3233 (NH), 2930, 2175 (CN), 1642, 1606, 1539, 1428, 767 cm^{-1}; ^1H NMR δ 1.96–2.05 (1H, m), 2.07–2.19 (3H, m), 2.49–2.56 (2H, m), 4.53 (2H, br s, NH_2), 5.97 (1H, d, J=5.5 Hz), 6.87 (1H, d, J=5.5 Hz). MS *m/z* (%) 146 (M^+, 40), 118 (100), 91 (18). Calcd for $C_9H_{10}N_2$: M,

146.0844. Found: *m/z* 146.0849. Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16%. Found: C, 73.62; H, 6.89; N, 18.74%.

3.1.3. 2-Cyanobicyclo[3.3.0]oct-1-en-3-one (10). To a solution of **9** (300 mg; 2.05 mmol) in acetic acid (117 mL) were added phosphoric acid (85%; 52 mL) and water (14 mL). The reaction mixture was stirred and heated under reflux for 1 h. The reaction mixture was neutralized with 10% aq NaOH and the whole was extracted with $CHCl_3$ and the organic layer was washed with brine. The organic layer was dried over $MgSO_4$ and the product was purified by silica gel flash column chromatography to give 300 mg (99%) of **10** as a colorless oil; IR (neat) 2971, 2229 (CN), 1724 (CO), 1642, 1270, 1257 cm^{-1}; ^1H NMR δ 1.24–1.33 (1H, m), 2.08–2.26 (3H, m), 2.29–2.34 (1H, m), 2.79–2.92 (3H, m), 3.06–3.12 (1H, m); ^{13}C NMR δ 202.89 (C), 202.35 (C), 112.01 (C), 111.75 (C), 47.05 (CH), 41.69 (CH_2), 30.68 (CH_2), 27.39 (CH_2), 25.15 (CH_2). MS *m/z* (%) 147 (M^+, 100), 119 (71), 104 (47), 91 (33), 81 (25), 79 (15).

3.1.4. 2-Cyanobicyclo[3.3.0]octan-3-one (12). To a solution of **10** (450 mg; 3.06 mmol) in methanol (38 mL) was added 10% Pd on carbon (540 mg). The reaction mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 1 h. The suspension was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to dryness to afford **12** (446 mg, 99%) as a colorless oil (about 1:1 diastereomeric mixture); IR (neat) 2955, 2872, 2246 (CN), 2201 (CN), 1752 (CO), 1670, 1634, 1451, 1381, 1134 cm^{-1}; ^1H NMR δ 1.40 (0.5H, sextet, J=7.0 Hz), 1.51–1.60 (1H, m), 1.64–1.87 (1.5H, m), 1.99–2.07 (3H, m), 2.30 (0.5H, dd, J=19.3, 4.3 Hz), 2.65–2.84 (2.5H, m), 2.94–3.00 (1H, m), 3.05 (0.5H, d, J=9.2 Hz), 3.63 (0.5H, d, J=8.9 Hz); ^{13}C NMR δ 207.20 (C), 207.15 (C), 116.71 (C), 115.89 (C), 45.40 (CH), 44.84 (CH), 44.76 (CH), 42.91 (CH_2), 42.44 (CH_2), 42.27 (CH), 38.16 (CH), 37.68 (CH), 33.36 (CH_2), 32.83 (CH_2), 31.78 (CH_2), 29.81 (CH_2), 24.90 (CH_2), 24.84 (CH_2). MS *m/z* (%) 149 (M^+, 95), 120 (93), 106 (33), 81 (88), 67 (100), 55 (71), 39 (63). Calcd for $C_9H_{11}NO$: M, 149.0840. Found: *m/z* 149.0844.

3.1.5. Bicyclo[3.3.0]octan-3-one (13). To a solution of **12** (280 mg; 1.88 mmol) in acetic acid (100 mL) were added phosphoric acid (85%; 40 mL) and water (13 mL). The reaction mixture was stirred and heated under reflux for 23 h. The reaction mixture was neutralized with 10% aq NaOH. The whole was extracted with $CHCl_3$ and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a yellow oil. The product was purified by silica gel flash column chromatography to give 91.7 mg (39%) of **13** as a colorless oil; IR (neat) 2950, 2868, 1740 (CO), 1450, 1405, 1375, 1233 cm^{-1}; ^1H NMR δ 1.37–1.44 (2H, m), 1.59–1.68 (1H, m), 1.72–1.80 (1H, m), 1.94 (2H, m), 2.01, 2.05 (each 1H, d, J=4.3 Hz), 2.46, 2.51 (each 1H, br d, J=9.8 Hz), 2.67–2.74 (2H, m); ^{13}C NMR δ 221.41 (C), 44.74 (CH_2), 39.66 (CH), 33.46 (CH_2), 25.53 (CH_2). MS *m/z* (%) 124 (M^+, 58), 95 (18), 81 (100), 67 (56), 54 (73), 39 (40). Calcd for $C_8H_{12}O$: M, 124.0888. Found: *m/z* 124.0892.

3.1.6. 2-Allyloxy-6a-phenyl-3,3a,4,5,6,6a-hexahydropentalene-1-carbonitrile (17). To a suspension of cuprous iodide (64.7 mg; 0.340 mmol) in dry THF (0.7 mL) was added phenylmagnesium bromide (0.23 mL of 3 M solution in diethyl ether; 0.68 mmol) at 0 °C. The suspension was stirred for 1 h and **10** (20 mg; 0.136 mmol) in 0.8 mL of dry THF followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.156 mL; 0.680 mmol) were added slowly to the organocuprate suspension. The reaction mixture was stirred for 2.5 h at 0 °C and allowed to warm to room temperature over 30 min. To the reaction mixture was added methyllithium (0.15 mmol) at 0 °C and the reaction mixture was stirred for 30 min. Allyl iodide (0.062 mL; 0.680 mmol) and hexamethylphosphoramide (0.243 mL; 0.136 mmol) were added to the reaction mixture and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by adding satd aq NH_4Cl and the whole was extracted with $CHCl_3$ and the organic layer was washed with satd aq NH_4Cl. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography to give **17** (23.5 mg; 65%) as a colorless oil; IR (neat) 2926, 2856, 2205 (CN), 1627, 1494, 1447, 1378, 1339, 1259, 1035, 977 cm^{-1}; ^1H NMR δ 1.51–1.57 (1H, m), 1.71–1.79 (1H, m), 1.80–1.88 (1H, m), 1.98–2.12 (2H, m), 2.24–2.27 (1H, m), 2.30 (1H, dd, J=18.0, 2.0 Hz), 2.68 (1H, ddt, J=9.0, 3.6, 2.0 Hz), 3.03 (1H, dd, J=18.0, 8.9 Hz), 4.79–4.87 (2H, m), 5.32 (1H, dq, J=10.5, 1.3 Hz), 5.40 (1H, dq, J=17.5, 1.5 Hz), 5.97 (1H, dq, J=17.3, 5.3 Hz), 7.21–7.24 (1H, m), 7.33, 7.34 (each 2H, s); ^{13}C NMR δ 169.78 (C), 146.57 (C), 131.91 (CH), 128.50 (CH), 126.50 (CH), 125.98 (CH), 121.75 (C), 118.56 (CH_2), 89.26 (C), 71.47 (CH_2), 64.00 (C), 46.51 (CH), 40.78 (CH_2), 38.06 (CH_2), 36.20 (CH_2), 25.65 (CH_2). MS *m/z* (%) 265 (M^+, 85), 236 (100), 224 (46), 196 (32), 182 (31), 167 (12), 154 (23), 141 (18), 127 (21), 115 (27). Calcd for $C_{18}H_{19}NO$: M, 265.1466. Found: *m/z* 265.1472.

3.1.7. 2-Oxo-1-(2-oxopropyl)octahydropentalene-1-carbonitrile (18). To a suspension of sodium hydride (10 mg; 0.24 mmol) in dry THF (4 mL) was added a solution of **12** (30 mg; 0.2 mmol) in dry THF (0.5 mL) at −78 °C and the reaction mixture was stirred for 30 min. Bromoacetone (0.09 mL; 0.96 mmol) was added to the reaction mixture and the solution was stirred for 3 h. Temperature of the reaction mixture was gradually allowed to warm to room temperature over 2 h and the reaction mixture was further stirred at room temperature for 30 min. The reaction was quenched by satd aq NH_4Cl. The whole was extracted with $CHCl_3$ and the organic layer was washed once with water. The solvent was evaporated under vacuum and the residue was purified by silica gel column chromatography to give **18** (32.8 mg; 79%) as a colorless oil; IR (neat) 2958, 2873, 2238 (CN), 1751, 1721 (CO), 1403, 1364, 1173, 1149, 1042 cm^{-1}; ^1H NMR δ 1.51 (1H, sextet, J=7.0 Hz), 1.65–1.73 (1H, m), 1.87–1.95 (2H, m), 1.97–2.11 (2H, m), 2.18 (3H, s), 2.30 (1H, dd, J=19.2, 6.4 Hz), 2.63–2.68 (1H, m), 2.78 (1H, sextet, J=8.0 Hz), 2.88 (1H, dd, J=19.2, 9.3 Hz), 3.15, 3.21 (each 1H, d, J=18.0 Hz); ^{13}C NMR δ 209.90 (C), 202.98 (C), 117.70 (C), 50.07 (C), 49.02 (CH_2), 48.13 (CH), 43.19 (CH_2), 37.69 (CH), 33.31 (CH_2), 30.54 (CH_2), 29.61 (CH_2), 25.71 (CH_3). MS *m/z* (%) 205 (M^+, 11), 162 (22), 148 (100), 134 (27), 120 (10), 92 (10), 43 (74). Calcd for $C_{12}H_{15}NO_2$: M, 205.1102. Found: *m/z* 205.1112.

3.1.8. 2-Hydroxy-2-phenyl-2,3,3a,4,5,6-hexahydropentalene-1-carbonitrile (19). Phenylmagnesium bromide (0.048 mL of 3 M solution in diethyl ether; 0.143 mmol) was added to a solution of **10** (10 mg; 0.068 mmol) in dry THF (0.36 mL) at 0 °C. The reaction mixture was stirred for 5 h and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed once with water and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give 13.4 mg (88%) of **19** as a colorless oil; IR (neat) 3436 (OH), 2962, 2928, 2857, 2216 (CN), 1665, 1449, 1069 cm^{-1}; ^1H NMR δ 1.25–1.33 (2H, m), 1.99–2.07 (3H, m), 2.12–2.19 (1H, m), 2.51–2.65 (2H, m), 2.71 (1H, dd, J=12.5, 7.1 Hz), 2.88–2.94 (1H, m), 7.31–7.34 (1H, m), 7.37–7.40 (2H, m), 7.45–7.47 (2H, m); ^{13}C NMR δ 175.63 (C), 143.33 (C), 128.81 (CH), 128.18 (CH), 124.84 (CH), 115.26 (C), 110.00 (C), 76.60 (C), 50.23 (CH), 49.60 (CH_2), 31.47 (CH_2), 27.16 (CH_2), 25.29 (CH_2). MS m/z (%) 225 (M^+, 100), 207 (23), 196 (49), 182 (72), 105 (87), 77 (81), 51 (31). Calcd for $C_{15}H_{15}NO$: M, 225.1153. Found: m/z 225.1157.

3.1.9. 3,3-Di(ethoxymethyl)cyclobutanone (21a). A solution of **20** (1.41 g; 6.35 mmol) in dry THF (2 mL) was added to a suspension of sodium hydride (0.76 g; 19.1 mmol) in dry THF (40 mL) at room temperature. After the reaction mixture was stirred for 5 min, iodoethane (2.54 mL; 31.8 mmol) was added. The whole was stirred overnight and the reaction was quenched by satd aq NH_4Cl. The reaction mixture was extracted with $CHCl_3$. The organic layer was washed with water and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography to give (3,3-bisethoxymethyl)cyclobutyl benzyl ether (1.52 g; 86%) as a colorless oil.

To a solution of this product (1.52 g; 5.45 mmol) in methanol (30 mL) was added 10% Pd on carbon (1.82 g). The reaction mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 3 h. The suspension was filtered thought a pad of Celite. The filtrate was evaporated under reduced pressure to dryness to afford (3,3-bisethoxymethyl)-cyclobutanol (1.00 g; 97%) as a colorless oil.

A solution of IBX (3.01 g; 10.7 mmol) in 22 mL of DMSO was stirred for 20 min. Cyclobutanol (1.01 g; 5.37 mmol) was added to the solution and the reaction mixture was stirred for 1.5 h. The reaction mixture was diluted with ether and the solution was washed twice with water and dried over $MgSO_4$. The organic layer was evaporated under vacuum and the residue was purified by silica gel column chromatography to give **21a** (847 mg; 85%) as a colorless oil; IR (neat) 2977, 2932, 2867, 1789 (CO), 1379, 1356, 1112 cm^{-1}; ^1H NMR δ 1.20 (6H, t, J=7.0 Hz), 2.90 (4H, s), 3.53 (4H, s), 3.53 (4H, q, J=7.0 Hz). MS m/z (%) 186 (M^+, 5), 158 (67), 111 (27), 99 (38), 85 (100), 71 (38), 57 (61), 55 (100). Calcd for $C_{10}H_{18}O_3$: M, 186.1255. Found: m/z 186.1250.

3.1.10. 7,7-Dimethyl-6,8-dioxaspiro[3.5]nonan-2-one (21b). To a solution of **20** (50 mg; 0.225 mmol) in dry acetone (2.3 mL) were added pyridinium p-toluenesulfonate (16.8 mg; 0.068 mmol) and magnesium sulfate at room temperature. The whole was stirred for 3 h and the reaction was neutralized by satd aq $NaHCO_3$. The whole was extracted with $CHCl_3$. The organic layer was evaporated under vacuum and the residue was purified by silica gel column chromatography to give 2-benzyloxy-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane (49.8 mg; 84%) as a colorless oil.

To a solution of the acetal (30 mg; 0.114 mmol) in methanol (3 mL) was added 10% Pd on carbon (40 mg). The reaction mixture was stirred at room temperature under H_2 atmosphere (1 atm) for 2 h. The suspension was filtered through a pad of Celite. The filtrate was evaporated under reduced pressure to dryness to afford 7,7-dimethyl-6,8-dioxaspiro-[3.5]nonan-2-ol (17.7 mg; 90%) as a colorless oil.

To a solution of oxalyl chloride (3.7 mL; 43.5 mmol) in CH_2Cl_2 (75 mL) was added dropwise DMSO (4.6 mL; 65 mmol) at −78 °C. The solution was stirred at −78 °C for 10 min. The alcohol (1.5 g; 8.7 mmol) in 5 mL of CH_2Cl_2 was added slowly to the reaction mixture. After stirring for 15 min at −78 °C, the temperature was warmed to −45 °C and then the reaction mixture was stirred for 1 h. Et_3N (10 mL; 74 mmol) was added to the reaction mixture, and warmed to 0 °C and then stirred for 20 min. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed with water and dried, and the solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography to give **21b** (1.3 g; 88%) as colorless crystals; mp 58–59 °C (AcOEt–hexane); IR (KBr) 2995, 2945, 2868, 1780 (CO), 1377, 1271, 1194, 1074, 1032, 823 cm^{-1}; ^1H NMR δ 1.46 (6H, s), 2.88 (4H, s), 3.88 (4H, s). MS m/z (%) 157 (M^+, 98), 113 (30), 97 (46), 59 (100), 43 (85). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29%. Found: C, 63.49; H, 8.34%.

3.1.11. 3,3-Diethoxymethyl-1-[chloro(*p*-tolylsulfinyl)-methylidene]cyclobutane (22a). Colorless oil; IR (neat) 2975, 2930, 2867, 1399, 1378, 1356, 1113, 1089, 1062 (SO) cm^{-1}; ^1H NMR δ 1.20, 1.22 (each 3H, t, J=7.0 Hz), 2.42 (3H, s), 2.64–2.73 (2H, m), 2.97–3.04 (2H, m), 3.44–3.47 (4H, m), 3.52, 3.53 (each 2H, q, J=7.0 Hz), 7.32 (2H, d, J=8.0 Hz), 7.50 (2H, d, J=8.0 Hz). MS m/z (%) 356 (M^+, 35), 339 (97), 311 (46), 297 (60), 235 (67), 203 (54), 181 (38), 171 (35), 139 (92), 123 (78), 91 (75), 77 (62), 59 (100). Calcd for $C_{18}H_{25}ClO_3S$: M, 356.1213. Found: m/z 356.1213.

3.1.12. 6-Amino-3,3-bisethoxymethylspiro[3.4]octa-5,7-diene-5-carbonitrile (23a). Colorless oil; IR (neat) 3350 (NH), 3232, 2975, 2930, 2868, 2178 (CN), 1646, 1608, 1422, 1110, 757 cm^{-1}; ^1H NMR δ 1.20, 1.24 (each 3H, t, J=7.0 Hz), 2.28 (2H, d, J=13.5 Hz), 2.37 (2H, d, J=13.8 Hz), 3.47–3.58 (8H, m), 4.53 (2H, br s, NH_2), 5.90, 6.89 (each 1H, d, J=5.4 Hz). MS m/z (%) 262 (M^+, 28), 203 (100), 157 (97), 118 (35), 85 (16). Calcd for $C_{15}H_{22}N_2O_2$: M, 262.1679. Found: m/z 262.1673.

3.1.13. 5,5-Bisethoxymethyl-2-oxo-2,3,3a,4,5,6-hexahydropentalene-1-carbonitrile (24a). Colorless crystals; mp 56–57 °C (AcOEt–hexane); IR (KBr) 2976, 2933, 2869, 2230 (CN), 1727 (CO), 1645, 1110 cm^{-1}; ^1H NMR δ 1.16, 1.19 (each 3H, t, J=6.9 Hz), 2.17–2.23 (2H, m), 2.77 (1H, dd, J=18.3, 6.7 Hz), 2.80, 2.86 (each 1H, d, J=19.0 Hz),

3.24, 3.30 (each 1H, d, J=9.0 Hz), 3.36–3.56 (8H, m); ^{13}C NMR δ 202.21 (C), 201.75 (C), 112.03 (C), 111.29 (C), 75.06 (CH_2), 74.89 (CH_2), 66.88 (CH_2), 66.78 (CH_2), 49.94 (C), 45.01 (CH), 42.24 (CH_2), 37.23 (CH_2), 35.02 (CH_2), 15.02 (CH_3), 14.90 (CH_3). MS m/z (%) 263 (M^+, 35), 217 (35), 171 (28), 160 (38), 146 (21), 85 (57), 59 (100). Calcd for $C_{15}H_{21}NO_3$: M, 263.1520. Found: m/z 263.1511. Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.43; H, 8.04; N, 5.22%. Found: C, 68.42; H, 8.04; N, 5.32%.

3.1.14. 2-[Chloro(*p*-tolylsulfinyl)methylene]-7,7-dimethyl-6,8-dioxaspiro[3.5]nonane (22b). Colorless crystals; mp 174–175 °C (AcOEt–hexane); IR (KBr) 2992, 2861, 1388, 1367, 1231, 1200, 1085, 1059 (SO), 886, 828, 807 cm^{-1}; ^{1}H NMR δ 1.43, 1.44 (each 3H, s), 2.42 (3H, s), 2.59 (1H, dd, J=17.4, 3.0 Hz), 2.67 (1H, ddd, J=17.4, 3.6, 1.2 Hz), 2.94 (1H, dd, J=17.4, 3.0 Hz), 3.07 (1H, ddd, J=17.4, 3.6, 0.6 Hz), 3.78, 3.80 (each 1H, d, J=12.0 Hz), 3.82 (2H, s), 7.33, 7.50 (each 2H, d, J=7.8 Hz). MS m/z (%) 340 (M^+, 100), 325 (70), 235 (89), 123 (87), 91 (78), 77 (83), 43 (91). Calcd for $C_{17}H_{21}ClO_3S$: M, 340.0899. Found: m/z 340.0901. Anal. Calcd for $C_{17}H_{21}ClO_3S$: C, 59.90; H, 6.21; Cl, 10.40; S, 9.41%. Found: C, 59.82; H, 6.20; Cl, 10.38; S, 9.39%.

3.1.15. 2-Amino-10,10-dimethyl-9,11-dioxadispiro-[4.1.5.1]trideca-1,3-dienecarbonitrile (23b). Colorless amorphous; IR (KBr) 3413, 3360, 3246 (NH), 2991, 2937, 2856, 2178 (CN), 1667, 1622, 1542, 1426, 1195, 1065, 834 cm^{-1}; ^{1}H NMR δ 1.41 (6H, s), 2.25, 2.33 (each 2H, br d, J=13.7 Hz), 3.86, 3.91 (each 2H, s), 4.58 (2H, br s, NH_2), 5.98, 6.65 (each 1H, d, J=5.5 Hz). MS m/z (%) 246 (M^+, 60), 231 (50), 171 (62), 157 (100), 132 (26), 118 (74), 43 (45). Calcd for $C_{14}H_{18}N_2O_2$: M, 246.1366. Found: m/z 246.1359.

3.1.16. Diacetate (24b). Colorless oil; IR (neat) 2955, 2231 (CN), 1739 (CO), 1651, 1384, 1367, 1232, 1040 cm^{-1}; ^{1}H NMR δ 2.09 (3H, s), 2.12 (3H, s), 2.24–2.29 (2H, m), 2.79 (1H, d, J=19.5 Hz), 2.84 (1H, dd, J=18.6, 7.0 Hz), 2.91 (1H, d, J=19.5 Hz), 3.35–3.41 (1H, m), 3.98, 4.10 (each 1H, d, J=11.0 Hz), 4.14, 4.19 (each 1H, d, J=11.0 Hz); ^{13}C NMR δ 200.97 (C), 197.54 (C), 170.67 (C), 170.56 (C), 112.41 (C), 111.47 (C), 67.27 (CH_2), 66.57 (CH_2), 47.78 (C), 44.17 (CH), 41.87 (CH_2), 36.30 (CH_2), 34.53 (CH_2), 20.73 (CH_3), 20.65 (CH_3). MS m/z (%) 291 (M^+, 1), 218 (27), 171 (58), 159 (23), 143 (21), 43 (100). Calcd for $C_{15}H_{17}NO_5$: M, 291.1107. Found: m/z 291.1108.

3.1.17. {1-[Chloro(*p*-tolylsulfinyl)methyl]cyclobutyl}acetonitrile (25). Acetonitrile (0.139 mL; 2.66 mmol) was added to a solution of n-BuLi (2.58 mmol) in 9 mL of dry THF at −78 °C with stirring. The solution was stirred for 10 min and a solution of **8** (200 mg; 0.831 mmol) in 3 mL of dry THF was added to the above reaction mixture. The reaction mixture was stirred for 10 min and the reaction was quenched by adding satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The products (less polar product **25-L** and more polar product **25-P**) were isolated by silica gel column chromatography to give **25-L** (167 mg; 71%) and **25-P** (56 mg; 24%) as colorless crystals.

Compound **25-L**: Mp 117–118 °C (AcOEt–hexane); IR (KBr) 2991, 2937, 2243 (CN), 1493, 1409, 1087, 1059, 1046 (SO), 1015, 810, 511 cm^{-1}; ^{1}H NMR δ 1.98–2.07 (1H, m), 2.14–2.20 (1H, m), 2.21–2.33 (2H, m), 2.40–2.47 (1H, m), 2.45 (3H, s), 2.66–2.72 (1H, m), 2.99, 3.21 (each 1H, d, J=16.8 Hz), 4.62 (1H, s), 7.37, 7.71 (each 2H, d, J=7.9 Hz). MS m/z (%) 281 (M^+, 2), 140 (100), 92 (41), 79 (13), 65 (9). Calcd for $C_{14}H_{16}ClNOS$: M, 281.0641. Found: m/z 281.0642. Anal. Calcd for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; Cl, 12.58; N, 4.97; S, 11.38%. Found: C, 59.68; H, 5.51; Cl, 12.58; N, 4.93; S, 11.31%. **25-P**. Mp 127–129 °C (AcOEt–hexane); IR (KBr) 2990, 2942, 2911, 2240 (CN), 1596, 1491, 1081, 1055 (SO), 817 cm^{-1}; ^{1}H NMR δ 2.02–2.11 (1H, m), 2.15–2.22 (1H, m), 2.26–2.31 (1H, m), 2.35–2.41 (2H, m), 2.44 (3H, s), 2.50–2.57 (1H, m), 2.91, 3.05 (each 1H, d, J=17.4 Hz), 4.49 (1H, s), 7.37, 7.50 (each 2H, d, J=8.3 Hz). MS m/z (%) 281 (M^+, 3), 140 (100), 92 (37), 79 (14), 65 (10). Calcd for $C_{14}H_{16}ClNOS$: M, 281.0642. Found: m/z 281.0634. Anal. Calcd for $C_{14}H_{16}ClNOS$: C, 59.67; H, 5.72; Cl, 12.58; N, 4.97; S, 11.38%. Found: C, 59.66; H, 5.54; Cl, 12.54; N, 4.95; S, 11.33%.

3.1.18. 6-Amino-7-phenylspiro[3.4]octa-5,7-diene-5-carbonitrile (26a). To a solution of LDA (0.442 mmol) in 1.5 mL of dry THF was added a solution of **25-L** (40 mg; 0.143 mmol) in 1.3 mL of dry THF at −78 °C and the reaction mixture was stirred for 30 min. To the reaction mixture was added lithium α-carbanion of phenylacetonitrile (1 mmol), which was generated from phenylacetonitrile and n-BuLi at −78 °C, through a cannula and the temperature of the reaction mixture was slowly allowed to warm to −40 °C over 1.5 h. The reaction was quenched by MeOH. The whole was extracted with $CHCl_3$. The product was isolated by silica gel column chromatography to give 24.7 mg (78%) of **26a** as colorless crystals; mp 93–95 °C (AcOEt–hexane); IR (KBr) 3377, 3226 (NH), 2929, 2853, 2177 (CN), 1638, 1548, 1414, 764, 703 cm^{-1}; ^{1}H NMR δ 2.01–2.08 (1H, m), 2.13–2.20 (1H, m), 2.22–2.27 (2H, m), 2.55–2.62 (2H, m), 4.67 (2H, br s, NH_2), 6.82 (1H, s), 7.35–7.45 (5H, m). MS m/z (%) 222 (M^+, 98), 194 (100), 166 (9). Calcd for $C_{15}H_{14}N_2$: M, 222.1157. Found: m/z 222.1159. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60%. Found: C, 80.88; H, 6.20; N, 12.60%.

3.1.19. 6-Amino-7-(4-methoxyphenyl)spiro[3.4]octa-5,7-diene-5-carbonitrile (26b). Colorless crystals; mp 144–145 °C (AcOEt–hexane); IR (KBr) 3426, 3339 (NH), 2969, 2932, 2176 (CN), 1650, 1605, 1555, 1507, 1461, 1445, 1248, 1177, 1028, 830, 602 cm^{-1}; ^{1}H NMR δ 2.00–2.08 (1H, m), 2.10–2.19 (1H, m), 2.21–2.26 (2H, m), 2.54–2.61 (2H, m), 3.84 (3H, s), 4.62 (2H, br s, NH_2), 6.75 (1H, s), 6.95, 7.29 (each 2H, d, J=10.6 Hz). MS m/z (%) 252 (M^+, 100), 224 (91), 209 (17), 193 (10). Calcd for $C_{16}H_{16}N_2O$: M, 252.1261. Found: m/z 252.1257. Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10%. Found: C, 76.15; H, 6.15; N, 11.15%.

3.1.20. 6-Amino-7-methylspiro[3.4]octa-5,7-diene-5-carbonitrile (26c). Colorless crystals; mp 114–115 °C (AcOEt–hexane); IR (KBr) 3446, 3353 (NH), 3252, 2971, 2931, 2171 (CN), 1660, 1647, 1560, 1454, 1420, 1243 cm^{-1}; ^{1}H NMR δ 1.87 (3H, d, J=1.5 Hz), 1.94–2.01 (1H, m), 2.08–2.15 (3H, m), 2.44–2.50 (2H, m), 4.55 (2H, br s, NH_2), 6.51 (1H, q, J=1.5 Hz). MS m/z (%) 160 (M^+,

33), 145 (12), 132 (100), 104 (8). Calcd for $C_{10}H_{12}N_2$: M, 160.0999. Found: *m/z* 160.1007.

3.1.21. 6-Amino-7-butylspiro[3.4]octa-5,7-diene-5-carbonitrile (26d). Colorless oil; IR (neat) 3428, 3354, 3250 (NH), 2956, 2930, 2856, 2169 (CN), 1679, 1649, 1559, 1432 cm^{-1}; ^1H NMR δ 0.94 (3H, t, J=7.3 Hz), 1.39 (2H, sextet, J=7.3 Hz), 1.54 (2H, quintet, J=7.7 Hz), 1.94–2.04 (1H, m), 2.06–2.17 (5H, m), 2.43–2.51 (2H, m), 4.60 (2H, br s, NH_2), 6.49 (1H, s). MS *m/z* (%) 202 (M^+, 48), 195 (20), 181 (23), 174 (24), 159 (100), 145 (20), 132 (50), 118 (12). Calcd for $C_{13}H_{18}N_2$: M, 202.1469. Found: *m/z* 202.1465.

3.1.22. 6-Amino-7-trityl-spiro[3.4]octa-5,7-diene-5-carbonitrile (26e). Colorless crystals; mp 235–236 °C (AcOEt–hexane); IR (KBr) 3455, 3368 (NH), 2931, 2185 (CN), 1633, 1596, 1548, 1490, 1442, 1399, 704 cm^{-1}; ^1H NMR δ 1.93–2.05 (2H, m), 2.14–2.18 (2H, m), 2.51–2.57 (2H, m), 3.91 (2H, br s, NH_2), 6.50 (1H, s), 7.14–7.16 (6H, m), 7.27–7.33 (9H, m). MS *m/z* (%) 388 (M^+, 97), 311 (38), 243 (100), 165 (55), 144 (11). Calcd for $C_{28}H_{24}N_2$: M, 388.1938. Found: *m/z* 388.1940.

3.1.23. 2-Phenylbicyclo[3.3.0]oct-1-en-3-one (27a). To a solution of **26a** (25 mg; 0.11 mmol) in 8 mL acetic acid were added phosphoric acid (85%; 3.3 mL) and water (0.75 mL). The reaction mixture was stirred and heated under reflux for 12 h. The reaction mixture was neutralized with 10% aq NaOH and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give 22.1 mg (99%) of **27a** as a colorless oil; IR (neat) 2962, 2930, 1692 (CO), 1627, 1595, 1133, 927, 765, 699 cm^{-1}; ^1H NMR δ 1.09–1.17 (1H, m), 2.07–2.13 (2H, m), 2.20–2.24 (1H, m), 2.26 (1H, dd, J=17.7, 3.6 Hz), 2.62–2.68 (1H, m), 2.81 (1H, dd, J=17.4, 7.2 Hz), 2.86–2.94 (2H, m), 7.28–7.31 (1H, m), 7.38–7.40 (2H, m), 7.59 (2H, d, J=7.8 Hz); ^{13}C NMR δ 208.75 (C), 185.38 (C), 134.56 (C), 131.79 (C), 128.30 (CH), 128.25 (CH), 127.73 (CH), 44.67 (CH), 42.95 (CH_2), 31.02 (CH_2), 27.31 (CH_2), 25.94 (CH_2). MS *m/z* (%) 198 (M^+, 100), 170 (57), 155 (24), 142 (65), 128 (23), 115 (31), 91 (10). Calcd for $C_{14}H_{14}O$: M, 198.1043. Found: *m/z* 198.1036.

3.1.24. 2-(4-Methoxyphenyl)bicyclo[3.3.0]oct-1-en-3-one (27b). Colorless oil; IR (neat) 2958, 2867, 1695 (CO), 1640, 1608, 1513, 1298, 1288, 1250, 1176, 1134, 1033, 831 cm^{-1}; ^1H NMR δ 1.09–1.16 (1H, m), 2.07–2.13 (2H, m), 2.20–2.27 (2H, m), 2.62–2.68 (1H, m), 2.81 (1H, dd, J=17.7, 6.0 Hz), 2.86–2.91 (2H, m), 3.84 (3H, s), 6.94, 7.58 (each 2H, d, J=9.0 Hz); ^{13}C NMR δ 209.11 (C), 183.62 (C), 159.07 (C), 133.96 (C), 129.48 (CH), 124.39 (C), 113.74 (CH), 55.26 (CH_3), 44.52 (CH_3), 42.91 (CH_2), 31.04 (CH_2), 27.32 (CH_2), 26.09 (CH_2). MS *m/z* (%) 228 (M^+, 100), 200 (45), 185 (12), 172 (33), 157 (13), 145 (11), 128 (14), 115 (13). Calcd for $C_{15}H_{16}O_2$: M, 228.1150. Found: *m/z* 228.1152.

3.1.25. 2-Methylbicyclo[3.3.0]oct-1-en-3-one (27c). Colorless oil; IR (neat) 2959, 2867, 1705 (CO), 1668, 1448, 1379, 1339, 1315, 1292, 1072, 1049 cm^{-1}; ^1H NMR δ 1.02–1.10 (1H, m), 1.70 (3H, s), 1.96–2.09 (3H, m), 2.13–2.17 (1H, m), 2.44–2.56 (2H, m), 2.63 (1H, dd, J=18.0, 6.0 Hz), 2.75–2.76 (1H, m); ^{13}C NMR δ 211.08 (C), 184.01 (C), 131.88 (C), 44.32 (CH), 41.60 (CH_2), 31.32 (CH_2), 25.58 (CH_2), 24.95 (CH_2), 8.57 (CH_3). MS *m/z* (%) 136 (M^+, 100), 108 (78), 93 (88), 79 (60), 53 (13), 39 (30). Calcd for $C_9H_{12}O$: M, 136.0888. Found: *m/z* 136.0897.

3.1.26. 2-Butylbicyclo[3.3.0]oct-1-en-3-one (27d). Colorless oil; IR (neat) 2957, 2861, 1702 (CO), 1664, 1466 cm^{-1}; ^1H NMR δ 0.90 (3H, t, J=7.2 Hz), 1.02–1.09 (1H, m), 1.26–1.32 (2H, m), 1.37–1.45 (2H, m), 2.00–2.11 (4H, m), 2.13–2.17 (1H, m), 2.21–2.26 (1H, m), 2.47–2.56 (2H, m), 2.62 (1H, dd, J=12.0, 6.0 Hz), 2.73–2.76 (1H, m); ^{13}C NMR δ 210.91 (C), 183.93 (C), 136.30 (C), 44.43 (CH), 41.80 (CH_2), 31.35 (CH_2), 30.21 (CH_2), 25.75 (CH_2), 25.15 (CH_2), 23.61 (CH_2), 22.66 (CH_2), 13.89 (CH_3). MS *m/z* (%) 178 (M^+, 63), 149 (100), 136 (62), 107 (26), 91 (23), 79 (31). Calcd for $C_{12}H_{18}O$: M, 178.1357. Found: *m/z* 178.1364.

3.1.27. 3-Triphenylmethylbicyclo[3.3.0]oct-1-en-3-one (27e). Colorless crystals; mp >300 °C (AcOEt–hexane); IR (KBr) 2926, 2859, 1706 (CO), 1624, 1492, 1444, 1253, 701 cm^{-1}; ^1H NMR δ 0.97–1.04 (1H, m), 1.59–1.67 (1H, m), 1.75–1.87 (2H, m), 1.93 (1H, dd, J=15.3, 3.6 Hz), 2.05–2.14 (2H, m), 2.66 (1H, dd, J=18.0, 6.6 Hz), 2.89–2.94 (1H, m), 7.14–7.17 (3H, m), 7.20–7.24 (12H, m); ^{13}C NMR δ 208.05 (C), 184.58 (C), 144.84 (C), 142.05 (C), 130.22 (CH), 127.41 (CH), 125.92 (CH), 59.56 (C), 45.45 (CH), 42.12 (CH_2), 31.47 (CH_2), 28.40 (CH_2), 25.83 (CH_2). MS *m/z* (%) 364 (M^+, 100), 287 (22), 165 (24). Calcd for $C_{27}H_{24}O$: M, 364.1828. Found: *m/z* 364.1825. Anal. Calcd for $C_{27}H_{24}O$: C, 88.97; H, 6.64%. Found: C, 88.66; H, 6.66%.

3.1.28. 3,3-Di(phenylsulfanyl)methylcyclobutyl benzyl ether (31). To a solution of **20** (1.0 g; 4.5 mmol) in 30 mL of dry THF at 0 °C was added diphenyl disulfide (4.72 g; 21.6 mmol) in 20 mL of dry THF followed by tri-*n*-butylphosphine (6.73 mL; 27 mmol). The reaction mixture was stirred for 10 min at 0 °C and the temperature of the reaction mixture was allowed to warm to room temperature and then stirred overnight. The reaction was quenched by 5% aq NaOH and the whole was extracted with $CHCl_3$. The organic layer was washed with water and the solvent was evaporated under vacuum to give a residue, which was purified by silica gel column chromatography to give **31** (1.81 g; 99%) as a colorless oil; colorless oil; IR (neat) 3059, 3030, 2968, 2928, 1583, 1480, 1454, 1438, 1350, 1251, 1111, 1090, 1060, 1026 cm^{-1}; ^1H NMR δ 1.95–1.99 (2H, m), 2.28–2.32 (2H, m), 3.23 (2H, s), 3.29 (2H, s), 4.06 (1H, quintet, J=6.8 Hz), 4.35 (2H, s), 7.13–7.18 (2H, m), 7.21–7.36 (13H, m). MS *m/z* (%) 406 (M^+, 51), 163 (27), 129 (17), 123 (41), 91 (100). Calcd for $C_{25}H_{26}OS_2$: M, 406.1425. Found: *m/z* 406.1424.

3.1.29. 3,3-Di(phenylsulfanyl)methylcyclobutanol (32). To a suspension of sodium iodide (1.11 g; 7.38 mmol) in dry CH_3CN (3 mL) was added dropwise a solution of TMSCl (0.58 mL; 7.38 mmol) at room temperature. The solution was stirred for 10 min. A solution of **31** (2.0 g; 4.92 mmol) in 2 mL of dry THF was added to the solution. The reaction mixture was stirred for 20 min and the reaction was quenched by adding MeOH. The whole was extracted

with $CHCl_3$. The organic layer was washed once with water and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give 873 mg (76%; calculated from consumed starting material) of **32** as a colorless oil; IR (neat) 3368 (OH), 3057, 2927, 1945, 1871, 1583, 1480, 1438, 1249, 1090, 1042, 738, 689 cm^{-1}; ^1H NMR δ 1.72 (1H, br s, OH), 1.87–1.93 (2H, m), 2.35–2.41 (2H, m), 3.18–3.26 (4H, m), 4.28–4.32 (1H, m), 7.15–7.28 (8H, m), 7.32–7.37 (2H, m). MS *m/z* (%) 316 (M^+, 100), 163 (30), 147 (12), 123 (49), 109 (28), 97 (18), 79 (23). Calcd for $C_{18}H_{20}OS_2$: M, 316.0953. Found: *m/z* 316.0952.

3.1.30. 3,3-Di(phenylsulfanyl)methylcyclobutanone (6). To a solution of oxalyl chloride (1.08 mL; 12.1 mmol) in CH_2Cl_2 (25 mL) was added DMSO (1.28 mL; 24.2 mmol) at −78 °C dropwise with stirring. The solution was stirred at −78 °C for 10 min. A solution of **32** (1.53 g; 4.84 mmol) in 13 mL of CH_2Cl_2 was added slowly to the above reaction mixture. After being stirred for 15 min at −78 °C, the temperature of the reaction mixture was allowed to warm to −45 °C and the reaction mixture was stirred for 1 h. Triethylamine (2.9 mL; 40.2 mmol) was added to the reaction mixture at the temperature, and it was warmed to 0 °C and then stirred for 20 min. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was washed with water and dried, and the solvent was evaporated under vacuum to give a residue, which was purified by silica gel column chromatography to give **6** (1.51 g; 99%) as a colorless oil; IR (neat) 3056, 2915, 1785 (CO), 1582, 1480, 1438, 1376, 1091, 1025 cm^{-1}; ^1H NMR δ 2.95 (4H, s), 3.39 (4H, s), 7.18–7.22 (2H, m), 7.25–7.29 (4H, m), 7.36–7.38 (4H, m). MS *m/z* (%) 314 (M^+, 100), 205 (13), 191 (43), 177 (11), 161 (68), 147 (16), 129 (56), 109 (43), 95 (20), 91 (18). Calcd for $C_{18}H_{18}OS_2$: M, 314.0798. Found: *m/z* 314.0798.

3.1.31. 3,3-Di(phenylsulfanyl)methyl-1-[chloro(*p*-tolylsulfinyl)methylidene]cyclobutane (33). Colorless oil; IR (neat) 3056, 2915, 1945, 1909, 1733, 1652, 1584, 1481, 1440, 1303, 1256, 1178, 1087, 1056 (SO) cm^{-1}; ^1H NMR δ 2.41 (3H, s), 2.71 (1H, dd, *J*=17.6, 2.8 Hz), 2.77 (1H, dd, *J*=17.6, 2.8 Hz), 3.03 (1H, dd, *J*=16.9, 2.8 Hz), 3.12 (1H, dd, *J*=16.9, 2.8 Hz), 3.27 (1H, d, *J*=12.5 Hz), 3.31 (1H, d, *J*=12.5 Hz), 3.32 (2H, s), 7.20–7.23 (2H, m), 7.26–7.31 (6H, m), 7.34–7.40 (4H, m), 7.47 (2H, d, *J*=8.3 Hz). MS *m/z* (%) 484 (M^+, 17), 467 (13), 361 (28), 235 (13), 199 (17), 161 (13), 139 (14), 123 (100), 109 (20), 91 (32). Calcd for $C_{26}H_{25}ClOS_3$: M, 484.0756. Found: *m/z* 484.0744.

3.1.32. {1-[Chloro(*p*-tolylsulfinyl)methyl]-3,3-bis(phenylsulfanylmethyl)cyclobutyl}acetonitrile (34). Colorless oil (about 2:1 diastereomeric mixture); IR (neat) 2931, 2245 (CN), 1732, 1584, 1481, 1440, 1256, 1090, 1062, 1026 (SO), 810, 741, 691 cm^{-1}; ^1H NMR (selected data are reported) δ 2.44 (2H, s, CH_3), 2.45 (1H, s, CH_3), 4.87 (0.66H, s), 4.90 (0.33H, s). MS *m/z* (%) 525 (M^+, 16), 386 (7), 140 (14), 123 (99), 110 (12), 91 (17). Calcd for $C_{28}H_{28}ClNOS_3$: M, 525.1022. Found: *m/z* 525.1024.

3.1.33. 6-Amino-7-methyl-2,2-di(phenylsulfanyl)methylspiro[3.4]octa-5,7-diene-5-carbonitrile (35). Colorless oil; IR (neat) 3352, 3233 (NH), 2927, 2174 (CN), 1652, 1563, 1480, 1438, 1416, 739, 690 cm^{-1}; ^1H NMR δ 1.83 (3H, d, *J*=1.6 Hz), 2.35 (2H, d, *J*=13.1 Hz), 2.40 (2H, d, *J*=13.1 Hz), 3.42, 3.44 (each 2H, s), 4.52 (2H, br s, NH_2), 6.38 (1H, t, *J*=1.6 Hz), 7.13–7.19 (2H, m), 7.23–7.28 (4H, m), 7.37–7.42 (4H, m). MS *m/z* (%) 404 (M^+, 67), 295 (19), 281 (92), 185 (99), 172 (41), 123 (53), 110 (18). Calcd for $C_{24}H_{24}N_2S_2$: M, 404.1378. Found: *m/z* 404.1371.

3.1.34. 2-Methyl-7,7-di(phenylsulfanyl)methylbicyclo[3.3.0]oct-1-en-3-one (36). Colorless oil; IR (neat) 3057, 2952, 2916, 1945, 1871, 1705 (CO), 1667, 1583, 1480, 1438, 1411, 1378, 1318, 1267, 1089, 1070, 1025, 740, 690 cm^{-1}; ^1H NMR δ 1.27 (1H, t, *J*=12.5 Hz), 1.66 (3H, t, *J*=1.3 Hz), 2.01 (1H, dd, *J*=18.0, 2.8 Hz), 2.27 (1H, dd, *J*=12.9, 8.2 Hz), 2.62 (1H, dd, *J*=18.0, 6.5 Hz), 2.65 (2H, s), 3.01 (1H, m), 3.17, 3.20 (each 1H, d, *J*=12.5 Hz), 3.31, 3.36 (each 1H, d, *J*=12.2 Hz), 7.16–7.21 (2H, m), 7.24–7.28 (4H, m), 7.29–7.33 (2H, m), 7.36–7.39 (2H, m); ^{13}C NMR δ 209.88 (C), 179.80 (C), 136.57 (C), 132.58 (C), 129.82 (CH), 129.80 (CH), 129.04 (CH), 128.99 (CH), 126.44 (CH), 126.38 (CH), 50.27 (C), 45.43 (CH_2), 44.73 (CH_2), 42.21 (CH), 41.93 (CH_2), 41.85 (CH_2), 37.22 (CH_2), 8.48 (CH_3). MS *m/z* (%) 380 (M^+, 73), 161 (17), 147 (12), 123 (99), 91 (13). Calcd for $C_{23}H_{24}OS_2$: M, 380.1268. Found: *m/z* 380.1270.

3.1.35. 2,7,7-Trimethylbicyclo[3.3.0]octan-3-one (37). To a solution of **36** (21 mg; 0.055 mmol) in EtOH (1.5 mL) was added Raney-Ni at room temperature. The suspension was stirred and heated under reflux for 4 h. The nickel was filtered off and the filtrate was diluted with hexane. The solution was washed three times with water and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give 7.1 mg (77%) of **37** as a colorless oil; IR (neat) 2953, 2935, 2866, 1739 (CO), 1458, 1365, 1157, 1063 cm^{-1}; ^1H NMR δ 0.99 (3H, s), 1.01 (3H, d, *J*=7.1 Hz), 1.06 (3H, s), 1.21 (2H, t, *J*=7.0 Hz), 1.43–1.47 (1H, m), 1.86 (1H, dd, *J*=18.8, 5.9 Hz), 1.92 (1H, ddd, *J*=13.4, 8.4, 1.7 Hz), 2.45–2.51 (1H, m), 2.63 (1H, ddd, *J*=18.7, 10.8, 1.8 Hz), 2.69–2.76 (1H, m), 2.88–2.96 (1H, m). MS *m/z* (%) 166 (M^+, 66), 149 (61), 123 (28), 109 (100), 95 (43), 83 (34), 69 (76), 55 (80). Calcd for $C_{11}H_{18}O$: M, 166.1355. Found: *m/z* 166.1354.

3.1.36. 1-Allyl-1,5,5-trimethylhexahydropentalen-2-one (38). To a suspension of sodium hydride (3.3 mg; 0.138 mmol) in dry THF (0.3 mL) was added a solution of **37** (15.3 mg; 0.092 mmol) in dry THF (0.9 mL) at room temperature. After the reaction mixture was stirred for 30 min, allyl iodide (0.026 mL; 0.276 mmol) was added. The reaction mixture was stirred for 2 h and the reaction was quenched by satd aq NH_4Cl. The whole was extracted with $CHCl_3$. The organic layer was washed and dried, and the solvent was evaporated under vacuum to give a residue, which was purified by silica gel column chromatography to give **38** (12.8 mg; 67%) as a colorless oil; IR (neat) 2933, 2866, 1738 (CO), 1731, 1641, 1465, 1457, 1410, 1374 cm^{-1}; ^1H NMR δ 0.95 (3H, s), 0.97 (3H, s), 1.06 (3H, s), 1.12 (1H, t, *J*=12.5 Hz), 1.20 (1H, dd, *J*=13.3, 5.1 Hz), 1.44 (1H, ddd, *J*=12.5, 6.9, 1.5 Hz), 1.89–1.93 (2H, m), 2.07–2.16 (2H, m), 2.59–2.77 (3H, m), 5.03 (1H, dq, *J*=16.9, 1.4 Hz), 5.08 (1H, dq, *J*=13.1, 0.9 Hz), 5.70 (1H, ddt, *J*=17.2, 9.8, 7.3 Hz); ^{13}C NMR δ 222.71 (C), 133.48 (CH), 118.19 (CH_2), 52.51 (C), 50.01 (CH), 48.98

(CH_2), 44.53 (CH_2), 43.53 (CH_2), 40.21 (C), 34.18 (CH), 30.07 (CH_3), 28.55 (CH_3), 17.32 (CH_3). MS *m/z* (%) 206 (M^+, 53), 191 (12), 149 (29), 137 (21), 123 (100), 109 (25), 95 (35), 81 (34), 67 (24). Calcd for $C_{14}H_{22}O$: M, 206.1668. Found: *m/z* 206.1665.

3.1.37. 1,5,5-Trimethyl-1-(2-oxopropyl)hexahydropentalen-2-one (39). Oxygen was bubbled through a mixture of $PdCl_2$ (10.4 mg; 0.059 mmol) and CuCl (46.1 mg; 0.465 mmol) and water (0.3 mL). To this reaction mixture a solution of **38** (32 mg; 0.155 mmol) in DMF (1.7 mL) was added, and the reaction mixture was stirred at room temperature for 24 h with O_2 being bubbled through the mixture. The suspension was filtered through a pad of Celite. The organic layer was evaporated under vacuum and the residue was purified by silica gel column chromatography to give **39** (34.3 mg; 99%) as a colorless oil; IR (neat) 2953, 2866, 1735 (CO), 1717 (CO), 1459, 1397, 1365, 1196, 1158, 1076 cm^{-1}; ^1H NMR δ 0.96 (3H, s), 0.99 (3H, s), 1.08 (3H, s), 1.15 (1H, dd, J=12.8, 7.5 Hz), 1.30 (1H, t, J=11.8 Hz), 1.51 (1H, ddd, J=12.7, 7.7, 1.7 Hz), 1.88 (1H, ddd, J=12.9, 8.1, 1.8 Hz), 2.05 (1H, dd, J=18.7, 7.0 Hz), 2.10 (3H, s), 2.65–2.87 (5H, m); ^{13}C NMR δ 223.46 (C), 206.41 (C), 53.18 (CH_2), 49.19 (CH_2), 48.88 (CH), 48.81 (C), 43.93 (CH_2), 42.40 (CH_2), 40.72 (C), 35.46 (CH), 30.59 (CH_3), 29.59 (CH_3), 27.90 (CH_3), 20.58 (CH_3). MS *m/z* (%) 222 (M^+, 2), 165 (100), 109 (17), 95 (10), 55 (13). Calcd for $C_{14}H_{22}O_2$: M, 222.1618. Found: *m/z* 222.1615.

3.1.38. Linear triquinane (7). To a solution of **39** (20 mg; 0.09 mmol) in dry *t*-BuOH (0.45 mL) was added *t*-BuOK (8.4 mg; 0.135 mmol) in one portion. After being stirred for 10 min at room temperature, satd aq NH_4Cl was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic layer was washed and dried, and the solvent was evaporated under vacuum to give a residue, which was purified by silica gel column chromatography to give **7** (14.3 mg; 78%) as a colorless oil; IR (neat) 2953, 2867, 1713 (CO), 1635, 1465, 1414, 1366, 1224, 1189, 1151 cm^{-1}; ^1H NMR δ 0.96 (3H, s), 1.09 (3H, s), 1.11 (3H, s), 1.19–1.26 (1H, m), 1.43–1.54 (2H, m), 1.80 (1H, dd, J=12.1, 6.0 Hz), 2.23–2.31 (3H, m), 2.36–2.42 (1H, m), 2.77–2.82 (2H, m), 5.68 (1H, d, J=1.7 Hz); ^{13}C NMR δ 210.90 (C), 195.82 (C), 122.07 (CH), 52.78 (CH_2), 50.60 (CH), 49.53 (CH_2), 49.29 (C), 44.45 (CH), 43.83 (C), 40.32 (CH_2), 32.91 (CH_2), 29.00 (CH_3), 27.42 (CH_3), 24.62 (CH_3). MS *m/z* (%) 204 (M^+, 32), 189 (20), 176 (6), 161 (7), 147 (6), 133 (7), 119 (9), 108 (23), 95 (19), 80 (19), 79 (13). Calcd for $C_{14}H_{20}O$: M, 204.1512. Found: *m/z* 204.1512.

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