A Predictable Enantioselective Total Synthesis of (+)-Clavularin A

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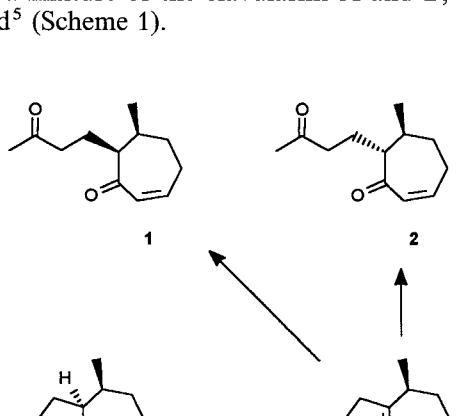
Cycloadduct **9** was transformed into vinylsilane **11d** in a conjugate addition–alkylation sequence. Epoxidation and subsequent hydrolysis provided the clavularin adduct **14**, which on flash vacuum pyrolysis (FVP) gave (+)-clavularin A (**1**) in 91% yield.

In 1983 Endo et al. isolated from the Okinawa soft coral *Clavularia koellikeri* two new compounds with significant cytotoxic and anticarcinogenic properties which were named clavularin A (**1**) and B (**2**).[1] The ambiguities in connection with their constitution and relative configuration were solved by synthesis[2–4] and by correlation with the unusual hydroazulene clavukerin A (**3**) which was shown by Kim and Pak to easily form hydroperoxide **4** which on acid treatment underwent a rearrangement to form a mixture of the clavularins A and B, albeit in low yield[5] (Scheme 1).



Scheme 1

The absolute configuration of these compounds remained an open question, however, because the X-ray data that had been collected from a diepoxide derived from clavukerin A only proved the relative configuration of this material.[6] This last problem was solved in 1993 when Tamura and his group published an application of their comparitively efficient auxiliary-directed conjugate addition process,[7,8] which provided a chiral acetal that yielded to X-ray structure determination.

Since we have recently demonstrated excellent diastereoselectivity in addition reactions to the enantiomerically pure Diels–Alder adducts **5** and **6** containing 5- and 6-membered rings,[9] we considered clavularin A an excellent testing ground to investigate also the additions to the conformationally more flexible seven-membered ring system (see **9**).

The special configuration and concave–convex conformation of adduct **9** was expected to guarantee high predictability for conjugate additions to the enone system which should give rise to the correct absolute configuration of clavularin A, thus proving that predictable enantioselective procedures may be used for independent assignment of absolute configurations.

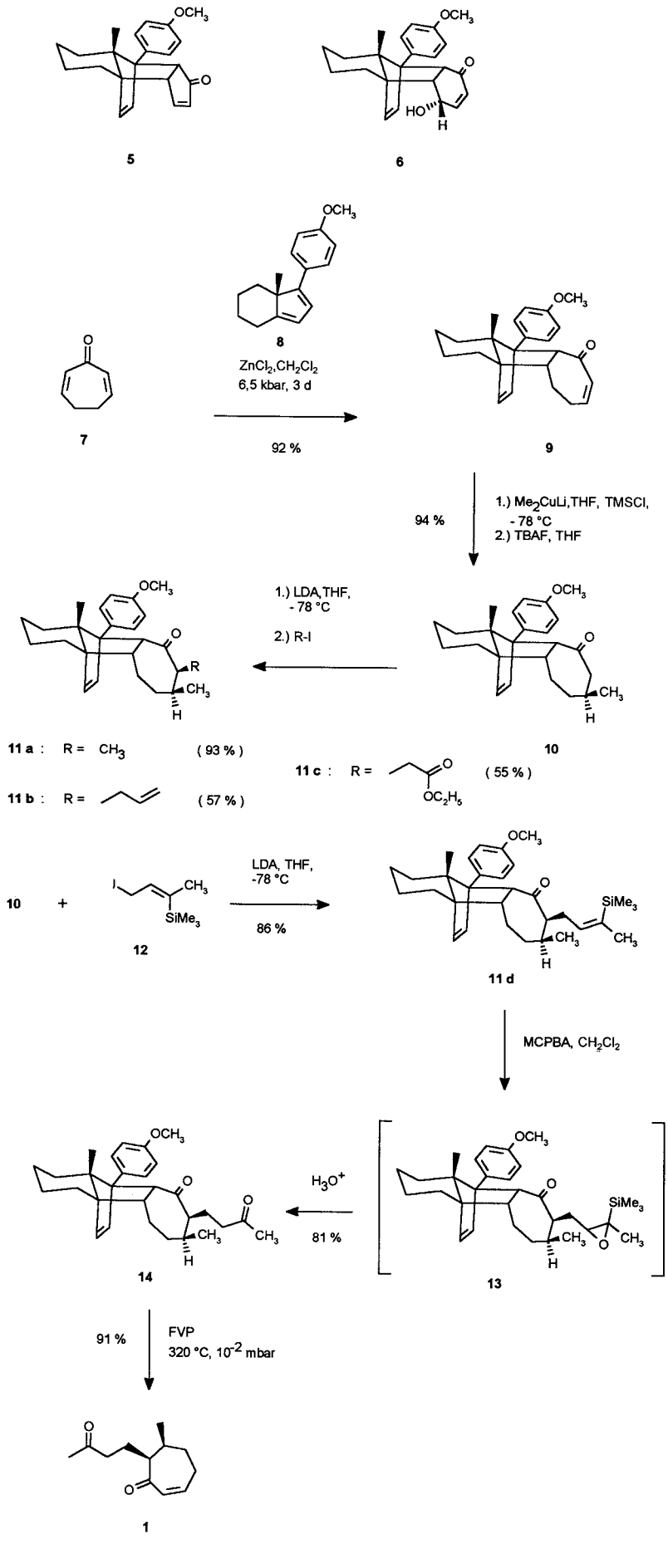
Krabbenhoft's straightforward procedure for the preparation of cycloheptadienone **7**[10] proved to be the method of choice for the generation of the dienophile, and the $ZnCl_2$ catalyzed cycloaddition to diene **8** provided adduct **9** in 91% yield. As expected, trimethylsilyl chloride mediated cuprate addition gave a 94% yield of ketone **10** after treatment with fluoride anions. It should be mentioned, however, that all our efforts to capture the intermediate enol derivatives in situ with methyl vinyl ketone or Stork's α-silylated version in a tandem process met with failure.

In contrast to this, various alkylation reactions easily provided the corresponding cis-alkylated products of type **11** with good to satisfactory yields (see Scheme 2). In this particular case the yield, however, was not as exciting as the fact that in all alkylations only one well defined stereoisomer was obtained, indicating the high β-selectivity of this process and proving the seven-membered ring to be a reliable candidate for diastereoselective transformations, too.

To ensure good results in this alkylation step we chose allylic iodide **12** for our purpose. This vinylsilane can be prepared in a straightforward way following Stork's procedure[11,12] and it gave cis-compound **11d** exclusively in 86% yield. The subsequent well described epoxidation–hydrolysis sequence[10–13] uneventfully led to diketone **14** in 81% yield (Scheme 3).

With this material, the stage was set for FVP to generate clavularin A, but to investigate a more simple case first, we studied the thermolysis of ketone **10** (Scheme 4). To our great delight this compound provided at 350°C and 10^{-2} mbar cycloheptenone **15** in 92% yield as a single enantiomer and the enantiomeric excess as shown by the use of the chiral shift reagent Eu(hfc)$_3$ in ^{1}H NMR spectroscopy to be greater than 98%. It must be mentioned, however, that although the above described alkylation of **15** produced the trans-dialkylated cycloheptenone **16** in 62% yield, the subsequent epoxidation–hydrolysis sequence, probably due to intramolecular conjugate addition processes, met with failure, thus proving the importance of the protection of this crucial double bond as a Diels–Alder adduct in the case of vinylsilane **11d**.

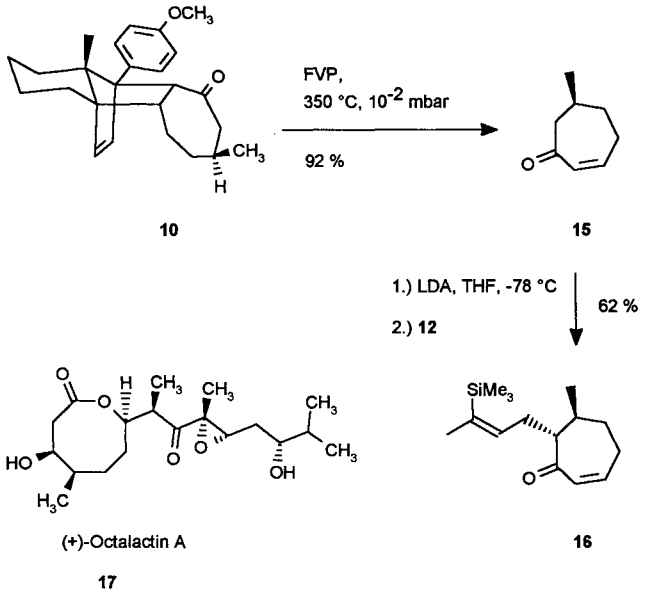
Cycloheptenone **15** is of further interest because its antipode was used recently by McWilliams and Clardy as a key chiral building block in their total synthesis of the cytotoxic compound (+)-octalactin A (**17**) and (+)-octalactin B.[14] These authors transformed the comparitively expensive (+)-citronellic acid in seven steps into *ent*-**15**. As the chiral cyclopentadiene **8** is easily accessible in both enantiomeric forms, we are able to provide enantiopure



Scheme 2

Scheme 3

15 as well as *ent*-**15** in three steps and very good yield starting from cycloheptadienone **7** which can be prepared without difficulties in large quantities. The diene **8** can be recovered without damage after the retro-Diels–Alder reaction and used in another cycloaddition.



Scheme 4

Encouraged by the high yield secured with cycloheptenone **15**, we next turned to FVP experiments with diketone **14** and were glad to immediately obtain clavularin A at 320 °C and 10^{-2} mbar in 91% yield (Scheme 3). The rotation value of + 78.9° confirmed the absolute configuration of this product as assigned by Tamura and his colleagues, thus proving the power of a predictable enantioselective synthesis for the determination of absolute configurations. Additionally these results prove the diastereoselectivity with cycloheptenone adducts to be as high and as reliable as with the corresponding 5- and 6-membered-ring systems.

Mps were determined on a Büchi melting point microscope and are uncorrected. UV spectra were measured in MeOH with a Beckmann 3600 instrument. IR spectra were measured with a Perkin-Elmer 581 spectrometer, and ^{1}H and ^{13}C NMR spectra with a Bruker WP 200 and WP 300. APT = attached proton test, (+) = C/CH_2; (−) = CH/CH_3. Mass spectra were determined with a Finnigan MAT 312 instrument and VG Autospec at 70 eV. For flash chromatography silica gel (30–60 mesh) (Baker) was used at 0.3 bar. All solvents were dried by the usual methods. Elemental analyses were obtained with a CHN rapid instrument (Heraeus). Petroleum refers to light petroleum (bp 50–70 °C). The high pressure reactions were performed in a Nova Swiss apparatus. For the retro-Diels–Alder reactions a special FVP apparatus was used.[15] (*E*)-(3-Iodo-1-methyl-1-propenyl)trimethylsilane was prepared according to Stork's procedure.[11,12]

Cycloheptenone 9:

A solution of cycloheptadienone **7**[10] (65 mg, 0.602 mmol) and diene **8**[16] (200 mg, 0.833 mmol) in 0.1 mL of dry CH_2Cl_2 was placed in a Teflon hose together with a 2.2 M solution of zinc chloride–Et_2O complex in CH_2Cl_2 (0.27 mL, 0.6 mmol) and pressurized for 3 d at 6.5 kbar in a high pressure autoclave. The mixture was diluted with CH_2Cl_2 and washed with sat. aq NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and evaporated. Chromatography (Et_2O–light petroleum, 1 : 3) of the oily residue yielded 192 mg (0.552 mmol, 92%) of **9** as a white solid (mp 143 °C). $[\alpha]_D^{20}$ − 38° (*c* = 1; $CHCl_3$).

UV (CH_3OH): λ = 225 nm.

IR ($CHCl_3$): ν = 2924 s, 2856 w, 1668 s, 1608 w, 1512 s, 1248 s, 1180 m, 968 w, 828 w cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.54 (br d, *J* = 14 Hz, 1 H), 0.75 (s, 3 H), 1.0–2.6 (m, 12 H), 3.77 (s, 3 H), 4.12 (d, *J* = 10 Hz, 1 H), 5.83 (d, *J* = 6 Hz, 1 H), 5.88 (dd, *J* = 2, 10 Hz, 1 H), 6.24–6.36 (m, 1 H), 6.36 (d, *J* = 6 Hz, 1 H), 6.84 (d, *J* = 9 Hz, 2 H), 7.13 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 14.6 (−), 21.3 (+), 23.5 (+), 25.0 (+), 27.0 (+), 28.3 (+), 32.9 (+), 48.7 (−), 55.1 (−), 59.2 (+), 60.4 (+), 63.6 (−), 66.1 (+), 113.2 (−), 127.5 (−), 131.2 (−), 131.6 (+), 135.8 (−), 138.5 (−), 142.1 (−), 157.7 (+), 202.7 (+).

MS (100 °C): *m*/*z* (%) = 349 (4/M^+ + 1), 348 (4/M^+), 280 (1), 266 (3), 241 (29), 240 (100), 225 (10), 197 (11), 165 (5), 135.2 (2), 121 (12), 108 (44), 84 (18), 65 (20).

Anal.: calc. C (82.72), H (8.10). Found C (82.93), H (8.13).

HRMS: *m*/*z* calc. for $C_{24}H_{28}O_2$, 348.2089; found, 348.2083.

Methylcycloheptanone 10:

CuI (820 mg, 4.305 mmol) was suspended in dry THF (12 mL), and at − 20 °C 1.6 M MeLi solution in Et_2O (5.383 mL, 8.613 mmol) was added dropwise. To this colourless solution cycloheptenone **9** (250 mg, 0.718 mmol) in dry THF (5 mL) was added slowly. The solution was cooled to − 40 °C and trimethylchlorosilane (0.1 mL, 0.788 mmol) hexamethyl phosphoramide (HMPA) (0.15 mL, 0.862 mmol) were added. The reaction mixture was stirred for 3 h at − 40 °C. Then the reaction was quenched with a mixture of sat. aq NH_4Cl and aq NH_3 (ca. 15 mL; pH 8). After addition of CH_2Cl_2 the two-phase system was stirred for 15 min. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the combined organic layers were washed with brine (15 mL) and water (15 mL), dried ($MgSO_4$) and evaporated. The obtained oil was dissolved in THF (3 mL) and 1 M tetrabutylammonium fluoride in THF/H_2O (1 mL, 1 mmol) was added. After stirring for 30 minutes at r.t. the mixture was diluted with water (15 mL) and extracted with CH_2Cl_2 (30 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL) and the combined organic layers were washed with brine (15 mL) and water (15 mL) dried ($MgSO_4$) and evaporated. Chromatography (Et_2O–light petroleum, 1 : 3) of the oily residue yielded 246 mg (0.676 mmol, 94%) of **10** as a white solid (mp 123 °C). $[\alpha]_D$ = − 6° (*c* = 1; $CHCl_3$).

IR ($CHCl_3$): ν = 2924 s, 2856 m, 1700 s, 1612 w, 1512 s, 1456 m, 1444 m, 1248 s, 1180 s, 828 w cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.54 (br d, *J* = 13 Hz, 1 H), 0.75 (s, 3 H), 0.96 (d, *J* = 7 Hz, 3 H), 1.0–2.5 (m, 15 H), 3.77 (s, 3 H), 4.08 (d, *J* = 10 Hz, 1 H), 5.76 (d, *J* = 6 Hz, 1 H), 6.37 (d, *J* = 6 Hz, 1 H), 6.83 (d, *J* = 9 Hz, 2 H), 7.10 (d, *J* = 9 Hz, 2 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 14.3 (−), 21.5 (+), 23.5 (+), 25.2 (+), 28.0 (+), 28.3 (+), 34.3 (−), 38.0 (+), 48.0 (−), 53.9 (+), 55.1 (−), 59.8 (+), 61.1 (+), 61.8 (+), 65.5 (+), 113.2 (−), 113.3 (−), 127.9 (−), 131.5 (+), 136.0 (−), 138.3 (−), 157.9 (+), 210.6 (+).

MS (50 °C): *m*/*z* (%) = 365 (3/M^+ + 1), 364 (5/M^+), 336 (3), 321 (2), 281 (3), 266 (4), 241 (22), 240 (100), 225 (11), 197 (11), 165 (6), 135 (3), 121 (10), 91 (6), 83 (12).

Anal.: calc. C (82.36), H (8.85). Found C (82.33), H (8.62).

HRMS: *m*/*z* calc. for $C_{25}H_{32}O_2$, 364.2402; found: 364.2418.

2,3-Dimethylcycloheptanone 11a:

To a solution of LDA (0.577 mmol) in dry THF (3 mL) was added dropwise at − 78 °C methylcycloheptanone **10** (70 mg, 0.192 mmol) in dry THF (2 mL). After addition of HMPA (0.05 mL, 0.288 mmol), the reaction mixture was stirred for 1 h at this temperature. Then methyl iodide (0.060 mL, 0.96 mmol) was added via a syringe. After 4 h the reaction was quenched with sat. aq NH_4Cl

(10 mL) and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Chromatography (Et_2O – light petroleum, 1:3) of the oily residue yielded 67 mg (0.177 mmol, 92%) of **11a** as a white solid (mp 171 °C). $[\alpha]_D^{20} = -1.9°$ ($c = 0.435$; $CHCl_3$).

IR (KBr): ν = 2948 s, 2920 s, 2852 m, 1700 s, 1612 w, 1512 s, 1456 m, 1440 m, 1244 s, 1180 m, 1032 m, 828 m cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.54 (br d, J = 13 Hz, 1 H), 0.76 (s, 3 H), 0.85 (m, 1 H), 0.93 (d, J = 7 Hz, 3 H), 1.00–1.20 (m, 2 H), 1.26 (d, J = 7 Hz, 3 H), 1.30–2.10 (m, 9 H), 2.20–2.50 (m, 2 H), 3.78 (s, 3 H), 4.26 (d, J = 10 Hz, 1 H), 5.76 (d, J = 6 Hz, 1 H), 6.38 (d, J = 6 Hz, 1 H), 6.83 (d, J = 9 Hz, 2 H), 7.08 (d, J = 9 Hz, 2 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 9.9 (–), 14.3 (–), 20.4 (–), 21.5 (+), 23.4 (+), 25.1 (+), 28.2 (+), 28.3 (+), 31.3 (+), 37.4 (–), 47.7 (–), 53.9 (–), 55.1 (–), 55.3 (–), 59.8 (+), 61.2 (+), 65.4 (+), 113.3 (–), 127.7 (–), 131.6 (+), 135.9 (–), 138.5 (–), 157.9 (+), 214.3 (+).

MS (70 °C): m/z (%) = 379 (2/M^+ + 1), 378 (3/M^+), 350 (2), 335 (2), 279 (2), 265 (3), 241 (19), 240 (100), 225 (13), 197 (18), 165 (5), 128 (4), 115 (31), 106 (16), 83 (9), 69 (9).

Anal. calc. C (82.48), H (9.06). Found C (82.22), H (8.93).

HRMS: m/z calc. for $C_{26}H_{34}O_2$, 378.2559; found, 378,2560.

2-Allyl-3-methylcycloheptanone 11b:
To a solution of LDA (0.687 mmol) in dry THF (3 mL) was added dropwise at –78 °C methylcycloheptanone **10** (130 mg, 0.357 mmol) in dry THF (3 mL). The reaction mixture was stirred for 2 h at this temperature. Then allyl bromide (0.100 mL, 1.156 mmol) was added via a syringe. After 4 h the reaction was quenched with sat. aq NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Chromatography (Et_2O – light petroleum, 1:3) of the oily residue yielded 82 mg (0.203 mmol, 57%) of **11b** as a colorless oil. $[\alpha]_D$ +2.1° (c = 0.125; $CHCl_3$).

IR (KBr): ν = 2956 m, 2924 s, 2856 w, 1692 s, 1612 w, 1516 s, 1460 w, 1444 w, 1248 s, 1180 s, 1040 w, 920 w, 828 w cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.47 (br d, J = 13 Hz, 1 H), 0.74 (s, 3 H), 0.85 (m, 1 H), 0.97 (d, J = 7 Hz, 3 H), 1.00–2.05 (m, 12 H), 2.25–2.70 (m, 3 H), 3.77 (s, 3 H), 4.17 (d, J = 10 Hz, 1 H), 5.22 (d, J = 16 Hz, 1 H), 5.24 (d, J = 10 Hz, 1 H), 5.78 (d, J = 6 Hz, 1 H), 5.75–6.00 (m, 1 H), 6.36 (d, J = 6 Hz, 1 H), 6.78 (d, J = 9 Hz, 2 H), 7.14 (d, J = 9 Hz, 2 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 14.3 (–), 20.9 (–), 21.5 (+), 23.5 (+), 25.1 (+), 28.2 (+), 28.7 (+), 28.9 (+), 31.9 (+), 37.7 (–), 47.8 (–), 55.1 (–), 56.7 (–), 58.5 (–), 59.9 (+), 60.9 (+), 65.9 (+), 113.0 (–), 116.7 (+), 128.4 (–), 131.4 (+), 136.4 (–), 137.4 (–), 138.0 (–), 157.8 (+), 213.3 (+).

MS (150 °C): m/z (%) = 405 (1/M^+ + 1), 404 (1/M^+), 377 (1), 366 (1), 347 (1), 280 (1), 266 (2), 241 (13), 240 (100), 225 (6), 197 (5), 165 (3), 149 (2), 121 (5), 99 (2), 91 (6), 67 (4).

HRMS: m/z calc. for $C_{28}H_{36}O_2$, 404.2715; found, 404.2702.

2-(Ethoxycarbonyl)methyl-3-methylcycloheptanone 11c:
To a solution of LDA (0.577 mmol) in dry THF (3 mL) was added dropwise at –78 °C methylcycloheptanone **10** (70 mg, 0.192 mmol) in dry THF (2 mL). After addition of HMPA (0.05 mL, 0.288 mmol) the reaction mixture was stirred for 2 h. Then ethyl iodoacetate (0.15 mL, 0.766 mmol) was added via a syringe. After 4 h the reaction was quenched with sat. aq NH_4Cl (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and evaporated. Chromatography (Et_2O – light petroleum, 1:3) of the oily residue yielded 48 mg (0.106 mmol, 55%) of **11c** as a colorless oil. $[\alpha]_D$ = +33.9° (c = 0.225; $CHCl_3$).

IR (KBr): ν = 2984 w, 2924 m, 2856 w, 1728 s, 1692 m, 1612 w, 1516 m, 1464 w, 1444 w, 1252 m, 1180 s, 1116 w, 1032 m, 828 w cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.49 (br d, J = 13 Hz, 1 H), 0.76 (s, 3 H), 0.96 (d, J = 7 Hz, 3 H), 1.10–1.45 (m, 4 H), 1.50–2.05 (m, 6 H), 2.36 (dt, J = 3, 9 Hz, 1 H), 2.50–3.00 (m, 6 H), 3.26 (dt, J = 7.7 Hz), 3.77 (s, 3 H), 4.05–4.30 (m, 4 H), 5.79 (d, J = 6 Hz, 1 H), 6.38 (d, J = 6 Hz, 1 H), 6.81 (d, J = 9 Hz, 2 H), 7.08 (d, J = 9 Hz, 2 H).

MS (100 °C): m/z (%) = 450 (1/M^+), 422 (1), 404 (1), 391 (1), 363 (1), 342 (1), 321 (1), 296 (4), 269 (4), 251 (2), 241 (100), 240 (2), 215 (24), 197 (8), 185 (25), 141 (33), 128 (8), 113 (20), 99 (9), 85 (8).

HRMS: m/z calc. for $C_{29}H_{38}O_4$ 450.2770; found 450.2770.

3-Methyl-2-[(3-trimethylsilyl)but-2-enyl]cycloheptanone 11d:
To a solution of LDA (1.500 mmol) in dry THF (5 mL) was added dropwise at –40 °C methylcycloheptanone **10** (450 mg, 1.236 mmol) in dry THF (5 mL). After addition of HMPA (0.05 mL, 0.288 mmol) the reaction mixture was stirred for 1 h. Then (*E*)-3-iodo-1-methylprop-1-enyl(trimethyl)silane (0.5 mL) was added via a syringe. After 3 h the reaction was quenched with brine (10 mL) and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with 2 N $Na_2S_2O_3$ (10 mL), dried ($MgSO_4$) and evaporated. Chromatography (Et_2O–light petroleum, 1:5) of the oily residue yielded 493 mg (1.006 mmol, 81%) of **11d** as a colorless oil. $[\alpha]_D$ = +30.3° (c = 0.430; $CHCl_3$).

IR (KBr): ν = 2956 s, 2856 m, 1692 m, 1612 w, 1516 m, 1248 s, 1180 w, 968 w, 836 s cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.13 (s, 9 H), 0.48 (br d, J = 14 Hz, 1 H), 0.70 (s, 3 H), 0.75–0.95 (m, 2 H), 0.98 (d, J = 7 Hz, 3 H), 1.10–1.90 (m, 13 H), 2.10–2.55 (m, 3 H), 2.75–2.95 (m, 1 H), 3.76 (s, 3 H), 4.04 (d, J = 9 Hz, 1 H), 5.67–5.78 (m, 1 H), 5.79 (d, J = 6 Hz, 1 H), 6.29 (d, J = 6 Hz, 1 H), 6.77 (d, J = 9 Hz, 2 H), 7.05 (d, J = 9 Hz, 2 H).

MS (100 °C): m/z (%) = 490 (3/M^+), 399 (3), 365 (3), 336 (3), 323 (6), 295 (3), 266 (4), 251 (5), 240 (100), 225 (10), 197 (13), 181 (10), 165 (9), 121 (8), 91 (12), 73 (87).

HRMS: m/z calc. for $C_{32}H_{46}O_2Si$, 490.3267; found, 490.3255.

Clavularin A Adduct 14:
To a solution of 2-(silylbutenyl)-3-methylcycloheptanone **11d** (160 mg, 0.356 mmol) in dry CH_2Cl_2 (12 mL) was added at 0 °C *m*-chloroperbenzoic acid (123 mg, 0.712 mmol) in dry CH_2Cl_2 (3 mL). The solution was stirred for 4 h at 20 °C. The reaction was quenched with 10% aq $NaHSO_3$ (6 mL) and extracted with CH_2Cl_2 (15 mL). The organic layers were washed with sat. aq Na_2CO_3 (15 mL) and brine (15 mL), dried ($MgSO_4$) and evaporated. Chromatography (Et_2O – light petroleum, 1:5) of the oily residue yielded 123 mg (0.284 mmol, 80%) of **14** as a colorless oil. $[\alpha]_D$ = +32° (c = 1.0; $CHCl_3$).

IR (KBr): ν = 2956 m, 2924 s, 1692 s, 1612 w, 1512 s, 1460 m, 1444 m, 1288 w, 1248 m, 1224 s, 1180 m, 832 w cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.42 (br d, J = 13 Hz, 1 H), 0.80 (s, 3 H), 0.94 (d, J = 7 Hz, 3 H), 1.05–2.25 (m, 15 H), 2.19 (s, 3 H), 2.30–2.50 (m, 3 H), 3.79 (s, 3 H), 4.12 (d, J = 10 Hz, 1 H), 5.80 (d, J = 6 Hz, 1 H), 6.42 (d, J = 6 Hz, 1 H), 6.82 (d, J = 9 Hz, 2 H), 7.13 (d, J = 9 Hz, 2 H).

MS (80 °C): m/z (%) = 435 (1/M^+ + 1), 434 (5/M^+), 407 (2), 355 (1), 266 (5), 256 (5), 240 (100), 225 (11), 197 (13), 183 (7), 157 (16), 143 79), 129 (44), 107 (33), 99 (17), 85 (70).

HRMS: m/z calc. for $C_{29}H_{38}O_3$, 434.2821; found, 434.2823.

Clavularin A (1):
Clavularin A adduct **14** (80 mg, 0.184 mmol) was placed in an FVP apparatus and sublimed at 140–220 °C and 10^{-2} mbar through a pyrolysis tube heated to 320 °C. After 30 min, all the starting material had sublimed and a 1:1 mixture of clavularin A **(1)** and diene **8** was trapped on a cold finger. Chromatographic purification (Et_2O –light petroleum, 1:3) yielded 30 mg (0.155 mmol; 84%) of **1** as a colorless oil. $[\alpha]_D$ = +78.0° (c = 0.5; $CHCl_3$) {Lit.[7] $[\alpha]_D$ = +59.2° (c = 0.37; $CHCl_3$)}; ee > 98% (shift experiment, ^1H NMR).

IR ($CHCl_3$): ν = 2960 m, 2932 m, 1712 s, 1668 m, 1444 w, 1396 w, 1356 w, 1260 m, 1232 m, 1156 w, 1096 w, 1016 w, 808 w cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.82 (d, J = 7 Hz, 3 H), 1.26 (m, 1 H), 1.60 (m, 1 H), 2.01–2.20 (m, 3 H), 2.10 (s, 3 H), 2.25–2.60 (m, 4 H), 2.80 (ddd, J = 4, 5, 10 Hz, 1 H), 6.02 (dd, J = 2, 12 Hz, 1 H), 6.76 (ddd, J = 4, 7, 12 Hz, 1 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 16.1 (−), 22.4 (+), 27.8 (+), 29.9 (−), 33.9 (−), 35.7 (+), 41.9 (+), 54.1 (−), 133.9 (−), 148.5 (−), 203.7 (+), 208.8 (+).

MS (25 °C): *m/z* (%) = 194 (8/M^+), 179 (4), 176 (4), 166 (4), 161 (6), 151 (15), 137 (53), 124 (18), 109 (47), 97 (6), 93 (44), 85 (15), 81 (50), 77 (19), 68 (100).

HRMS: *m/z* calc. for $C_{12}H_{18}O_2$, 194.1307; found, 194.1302.

(*S*)-6-Methyl-2-cycloheptenone (15):
Methylcycloheptanone **10** (450 mg, 1.236 mmol) was placed in an FVP apparatus and sublimed at 200 °C and 10^{-2} mbar through a pyrolysis tube heated to 350 °C. After 45 min all the starting material had sublimed and a 1:1 mixture of methylcycloheptenone **15** and diene **8** was trapped on a cold finger. Chromatographic purification (Et_2O–light petroleum, 1:3) yielded 141 mg (1.137 mmol; 92 %) of **15** as a slightly yellow oil. $[\alpha]_D^{20}$ = − 59° (*c* = 1,0; $CHCl_3$) {Lit.[14] $[\alpha]_D$ = + 64.6 (*c* = 1.09; $CHCl_3$)}, *R*-enantiomer. ee > 98 % (shift experiment, ^{1}H NMR).

IR ($CHCl_3$): ν = 2956 s, 2928 s, 2872 m, 1660 s, 1604 m, 1508 m, 1248 m, 1176 m, 832 w cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 7 Hz, 3 H), 1.45–1.65 (m, 1 H), 1.80–2.20 (m, 1 H), 2.30–2.50 (m, 3 H), 2.69 (dd, *J* = 5, 15 Hz, 1 H), 6.02 (dd, *J* = 1, 12 Hz, 1 H), 6.65 (ddd, *J* = 5, 12, 12 Hz, 1 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = 22.0 (−), 28.4 (+), 28.5 (−), 34.9 (+), 51.4 (+), 132.8 (−), 147.4 (−), 203.2 (+).

MS (25 °C): *m/z* (%) = 125 (3/M^+ + 1), 124 (18/M^+, 109 (18), 108 (20), 95 (31), 91 (6), 82 (12), 81 (100), 77 (13), 68 (54).

HRMS: *m/z* calc. for $C_8H_{12}O_1$, 124.0888; found, 124.0891.

***trans*-6-Methyl-3-trimethylsilylbut-2-enyl-2-cycloheptenone (16):**
To a solution of LDA (1.0 mmol) in dry THF (3 mL) was added dropwise at − 78 °C methylcycloheptenone **15** (60 mg, 0.484 mmol) in dry THF (2 mL). After addition of HMPA (0.05 mL, 0.288 mmol) the reaction mixture was stirred for 1 h. Then (*E*)-3-iodo-1-methylprop-1-enyltrimethylsilane (0.3 mL, 250 mg) was added via a syringe. After 2 h the reaction was quenched with brine and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were washed with 2 N $Na_2S_2O_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Chromatography (Et_2O –light petroleum, 1:5) of the oily residue yielded 75 mg (0.300 mmol, 62 %) of **16** as a colorless oil. $[\alpha]_D$ = − 10.7° (*c* = 0.575; $CHCl_3$).

IR ($CHCl_3$): ν = 2956 s, 2928 m, 1672 s, 1616 w, 1456 w, 1428 w, 1380 w, 1248 s, 1156 w, 1120 w, 952 w, 840 s cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.00 (s, 9 H), 1.07 (d, *J* = 7 Hz, 3 H), 1.65 (d, *J* = 1 Hz, 3 H), 1.55–1.90 (m, 3 H), 2.20–2.60 (m, 5 H), 5.58 (m, 1 H), 5.94 (ddd, *J* = 1, 1, 12 Hz, 1 H), 6.50 (m, 1 H).

^{13}C NMR (50 MHz, APT, $CDCl_3$): δ = − 2.1 (−), 14.5 (−), 20.2 (−), 28.0 (+), 30.1 (+), 33.2 (+), 33.9 (−), 60.4 (−), 131.9 (−), 136.3 (−), 137.6 (+), 144.5 (−), 206.3 (+).

MS (25 °C): *m/z* (%) = 251 (11/M^+ + 1), 250 (36/M^+), 235 (42), 221 (30), 208 (48), 193 (100), 177 (34), 168 (28), 153 (27), 145 (47), 134 (23), 124 (25), 117 (34), 105 (58), 91 (61).

HRMS: *m/z* calc. for $C_{15}H_{26}O_1Si_1$, 250.1753; found, 250.1764.

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