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A CONVENIENT ENTRY TO NEW C-7-MODIFIED COLCHICINOIDS THROUGH AZIDE ALKYNE [3+2] CYCLOADDITION: APPLICATION OF RING-CONTRACTIVE REARRANGEMENTS

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Abstract – Reliable procedures for the preparation of azides derived from colchicine (**1**), allocalchicine (**3**) and *N*-acetylcolchinol (**4a**) were developed. These azides were then employed in Cu-catalyzed Huisgen-Sharpless [3+2] cycloaddition (“click”) reactions with alkynes under microwave irradiation. The method developed opens a convenient and efficient access to libraries of new C-7-modified colchicinoids (triazole derivatives). In addition, a plausible mechanistic rationale for the colchicine-allocalchicine rearrangement is suggested.

INTRODUCTION

Colchicine (**1**), the main alkaloid of *Colchicum autumnale* (known as *meadow saffron* or *Herbstzeitlose* in german-speaking countries), was first isolated in pure form by Pelletier and Caventou in 1820¹ and its correct structure was proposed by Dewar only in 1945.² Colchicine is a powerful mitosis-inhibiting and anti-inflammatory agent used as a drug in the treatment of gout and Mediterranean fever.³ Its unique constitutional and stereostructural features, comprising a tropolone methyl ether (fused to a second seven-membered ring) and a chiral biaryl axis, configurationally “programmed” by the stereocenter at C-7, has challenged organic chemists for many decades.⁴ The first total synthesis of colchicine was accomplished by Eschenmoser and coworkers in 1959⁵ and since then various synthetic strategies were elaborated, mirroring the evolution of organic synthesis over the past 50 years.⁶ Interesting aspects of the chemistry of colchicine (**1**) are its facile acidic hydrolysis to colchiceine (**2**)⁷ and its base-induced ring-contractive rearrangement to its constitutional isomer allocalchicine (**3**) (Figure 1).⁸

This paper is dedicated to Professor Albert Eschenmoser on the occasion of his 85th birthday.

In addition, oxidative rearrangement/degradation of **2** leads to *N*-acetylcolchinol (**4a**)⁹ the phosphate of which (**4b**) has received much attention in recent years as a drug candidate named ZD6126.¹⁰

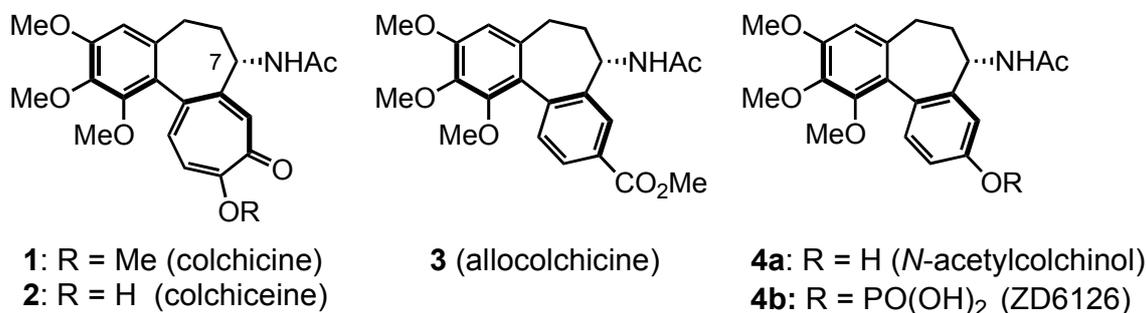
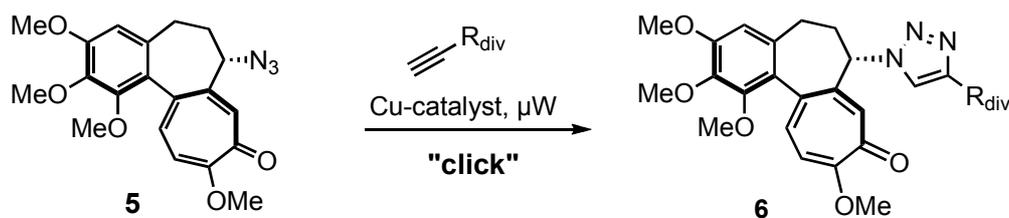


Figure 1

The biological activity of colchicine (and other colchinoids) is mainly connected to the inhibition of microtubule formation (tubulin polymerization), which leads to cell-cycle arrest and subsequent apoptosis. Therefore, **1** also represents a lead structure in the search for new anti-tumoral drugs.¹¹ While colchicine (**1**) itself is too toxic to be used in cancer therapy, the search for new derivatives with lower toxicity still represents a relevant challenge, and allicolchicine and colchinol derivatives (with a benzenoid ring C) are of particular interest in this context.¹²

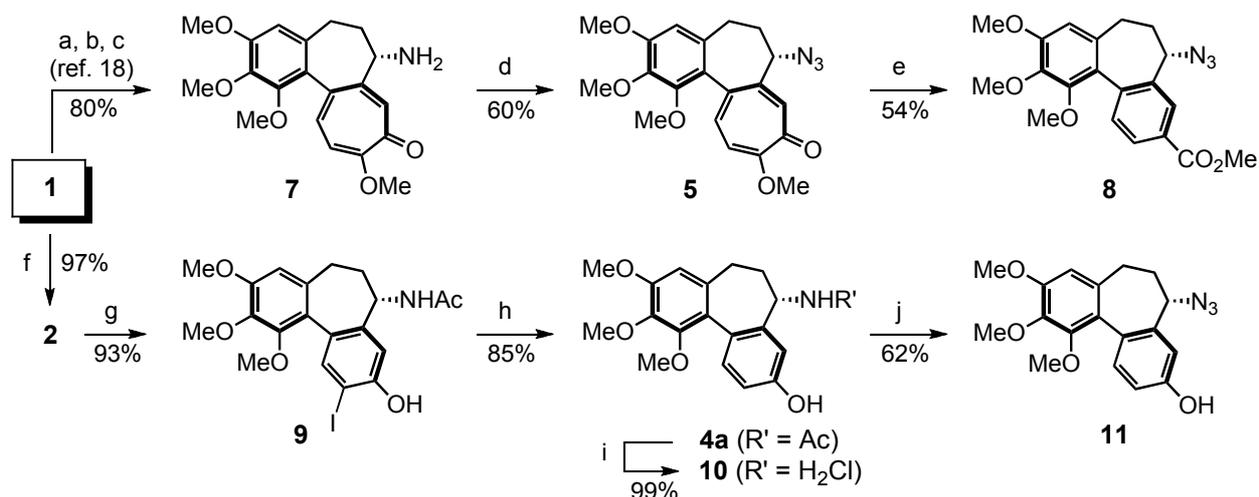
In the course of our own research in the field of colchicine chemistry¹³ we recently disclosed a click-conjugation approach allowing for a simple and fast diversification of the natural product **1** in position 7 (Scheme 1).¹⁴ The method is based on the colchicine-derived azide **5** which smoothly reacts with various alkynes in a Huisgen [3+2] cycloaddition¹⁵ under Cu-catalysis¹⁶ and microwave acceleration.¹⁷ The resulting triazoles of type **6** exhibited encouraging biological properties, and some were even more active than colchicine itself. We therefore were interested in a further expansion of the method and report herein efficient procedures also for the preparation of azides derived from allicolchicine (**3**) and *N*-acetylcolchinol (**4a**) and their use in the synthesis of the corresponding triazoles.



Scheme 1. Synthesis of C-7 derivatives of colchicine through click chemistry

RESULTS AND DISCUSSION

Starting from commercially available colchicine (**1**) the three azides **5**, **8** and **11** were prepared as shown in Scheme 2. As previously reported,¹⁴ the colchicine-related azide **5** was obtained *via* desacetylcolchicine (**7**)¹⁸ through direct diazo transfer with a freshly prepared solution of triflyl azide (TfN_3).¹⁹ The conversion of **5** into the allocolchicine-related azide **8** proceeded smoothly under the “classical conditions” of the colchicine-allocolchicine rearrangement, i.e. by heating with NaOMe in MeOH.^{8,20} The synthesis of the colchinol-related azide **11** started with the hydrolysis of **1** to colchiceine (**2**) by heating with HCl and AcOH.⁷ The oxidative degradation of **2** to the iodo-colchinol **9** was then achieved in high yield under the Windaus conditions⁹ (I_2 , KI, NaOH).²¹ After reductive deiodination of **9** with Zn in AcOH and subsequent acidic hydrolysis of the amide function, the resulting colchinol hydrochloride (**10**) was converted into the azide **11** using TfN_3 in the presence of a Cu(II)-catalyst.



Scheme 2. Preparation of the azides **5**, **8** and **11** starting from colchicine (**1**). Reagents and conditions: a) NEt_3 , Boc_2O , DMAP, CH_3CN , reflux, 3 h; b) NaOMe (20 mol%), MeOH, RT, 45 min; c) TFA, RT, 15 min; d) TfN_3 , CuSO_4 (1 mol%), K_2CO_3 , H_2O , MeOH, CH_2Cl_2 24 h; e) MeOH, NaOMe (2 equiv.), 75 °C, 1 h; f) 0.1 M HCl, AcOH, 100 °C, 3 h; g) NaOH, I_2 , KI, H_2O , 0 °C, 1.5 h; h) Zn, AcOH, 120 °C, 1 h; i) 0.2 M HCl, MeOH, 120 °C, 65 h; j) TfN_3 , CuSO_4 (1 mol%), NaHCO_3 , H_2O , MeOH, 2h.

The three azides **5**, **8**, and **11** were then employed in the Cu-catalyzed cycloaddition reactions with alkynes (compare Scheme 1) to give new C7-derivatives of colchicine, allocolchicine and colchinol (Figure 2). Under the previously optimized conditions (1 mol % $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$, 10 mol % sodium ascorbate, $\text{H}_2\text{O}/\text{tert-BuOH} = 1 : 1$, μW , 300W, 85 °C, 20 min) the triazoles **12** to **20** were obtained in typical yields of 80-95% after purification. As alkynes, we here used propargylic alcohol and some of its esters because our previous investigation¹⁴ suggested that the resulting products, especially the fatty acid derivatives (oleates, palmitates and laurates), should exhibit particularly interesting biological activities.

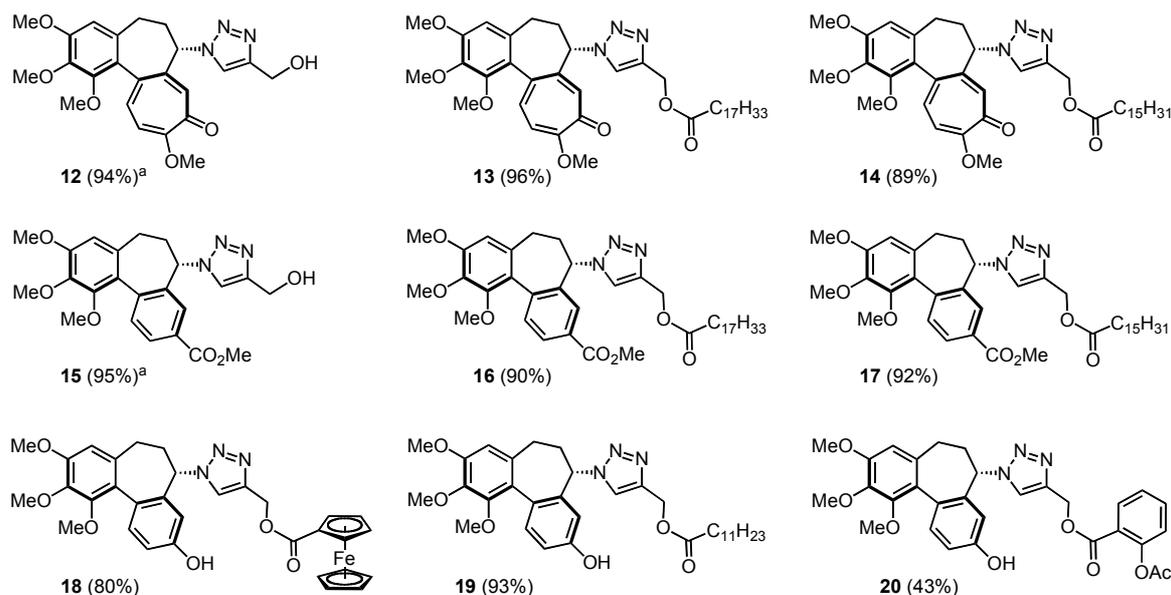
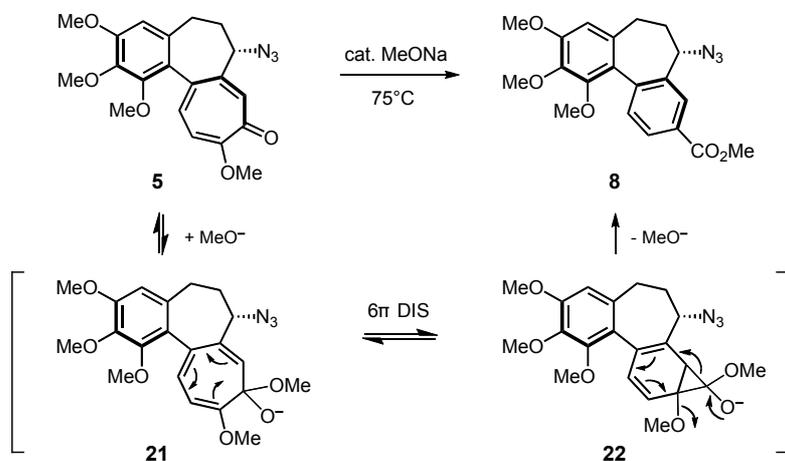


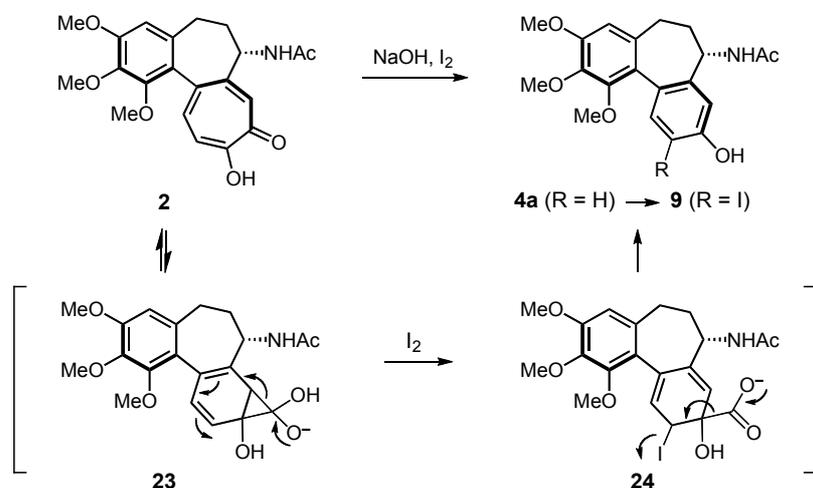
Figure 2. Triazoles prepared from the azides **5**, **8** and **11** through click-conjugation according to Scheme 1. ^aIn these cases 5 mol% (instead of 1 mol%) of CuSO₄ were used.

Having successfully exploited the long-known ring contractions in the synthesis of **8** and **11** as described above, we recognized that a satisfying mechanistic rationalization has never been published for these transformations.²² Therefore, we allow ourselves to suggest here a plausible mechanism for the colchicine-allocolchicine rearrangement (Scheme 3). We assume a (reversible) attack of a methoxide at the tropolone carbonyl group of **5** leading to a dearomatized intermediate **21**, which then undergoes a thermal disrotatory 6 π electrocyclicization to form a norcaradiene derivative (**22**). The cyclopropane ring is then fragmented in a Favorsky-type process to yield the aromatic product **8** under methoxide elimination, probably via an anionic Meisenheimer-type intermediate (not shown).²³



Scheme 3. Proposed mechanism of the colchicine-allocolchicine rearrangement (**5** to **8**)

In a related fashion, the oxidative transformation of colchicine (**2**) leading to colchinol derivatives is supposed to be initiated by a nucleophilic attack of a hydroxide ion to the tropolone carbonyl group and subsequent disrotatory 6π electrocyclicization (Scheme 4). In this case, however, opening of the resulting norcaradiene intermediate (**23**) can lead to an iodinated species of type **24**, which under elimination of CO_2 (and aromatization) would yield colchinol (**4a**). Indeed, if the reaction of **2** is performed only with one equivalent of iodine, significant amounts of colchinol (**4a**) are formed. To achieve high preparative yields, however, it is much more efficient to run the reaction under the Windaus conditions with an excess of iodine and to take into account the formation of the iodinated product **9** (compare Scheme 2), which then has to be de-iodinated in a separate additional operation.



Scheme 4. Proposed mechanism of the ring-contractive fragmentation of colchicine (**2**) to colchinols

CONCLUSION

Taking the “old” colchicine structure as a lead, the application of modern synthetic methodology opens new avenues to libraries of *C*-7-modified colchicinoids as promising molecules for biological investigations. In this context, we have developed reliable protocols for the preparation of azides derived from colchicine (**1**), allicolchicine (**3**) and *N*-acetylcolchinol (**4a**) and demonstrated their use in 1,3-dipolar cycloadditions with alkynes (click chemistry). Furthermore, we have suggested a consistent mechanistic rationale for the long-known ring-contractive rearrangements exploited in the semi-synthesis of allicolchicine and colchinol derivatives starting from **1**.

EXPERIMENTAL

General: *NMR spectra* were recorded on Bruker DRX 500 or Bruker DPX 300 instruments. Chemical shifts (δ) are given in ppm relative to the solvent reference as an internal standard (CDCl_3 , $\delta = 7.24$ ppm).

(^1H), $\delta = 77.0$ ppm (^{13}C)). The assignments are supported by HMBC, HMQC and H,H-COSY spectra. *Fourier transform infrared spectra (FT-IR)* were recorded on a *Perkin Elmer FT-IR Paragon 1000* spectrometer. *Melting points (mp)* were measured on *Büchi B-545* melting point apparatus and are uncorrected. *Mass spectra (MS)* were recorded on a *Finnigan Incos 50 Galaxy System (DIP-MS)*, high resolution mass spectra (HRMS) were recorded on a *Finnigan MAT 900 (HR-EI-MS)*. Microwave promoted reactions were carried out in a *CEM Discover* microwave synthesizer in sealed microwave flasks equipped with a stir bar. Flash chromatography was performed using silica 60 (230-400 mesh) supplied by *Merck*.

(aR,7S)-7-Azido-1,2,3,10-tetramethoxy-6,7-dihydrobenzo[a]heptalene-9(5H)-one (5)

To a solution of NaN_3 (4.44 g, 68.3 mmol) in 11 mL of water were added 18 mL of CH_2Cl_2 and the resulting suspension was cooled to 0 °C. After 5 min, 2.3 mL (13.7 mmol, 3.85 g) of Tf_2O were added dropwise. The mixture was stirred for 2 h at 0 °C before the phases were separated and the aqueous phase was re-extracted twice with 9 mL of CH_2Cl_2 . The combined organic solutions of triflyl azide were washed with sat. aqueous Na_2CO_3 and used directly in the next step.

A solution of the crude amine **7** (2.44 g, 6.83 mmol) in 20 mL of MeOH was diluted with 20 mL of water before 17.1 mg of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ (68 μmol , 1 mol%) and 1.41 g of K_2CO_3 (10.2 mmol) were added followed by additional 20 mL of MeOH. Then, the solution of triflyl azide (prepared as described above) was added dropwise. The resulting suspension was diluted with additional MeOH (ca. 10 mL) until a clear solution was formed. After 24 h the organic solvents were removed under reduced pressure and the remaining residue was poured into water and extracted with EtOAc (4x). The combined organic layers were washed with brine and dried over MgSO_4 and concentrated. The crude product was purified by column chromatography (EtOAc/cy-hex = 10:1) to give 1.58 g (4.12 mmol, 60 %) of the azide **5** as a yellowish solid. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ [ppm] = 1.80-1.85 (m, 1 H, H-6), 2.31-2.50 (m, 3 H, H-6, 2 x H-5), 3.62 (s, 3 H, OMe), 3.86 (s, 6 H, 2 x OMe), 4.23 (dd, $^3J = 11.4$ Hz, $^3J = 6.0$ Hz, 1 H, H-7), 6.49 (s, 1 H, H-4), 6.75 (d, $^3J = 11.1$ Hz, 1 H, H-11), 7.16 (d, $^3J = 11.0$ Hz, 1 H, H-12), 7.59 (s, 1 H, H-8). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ [ppm] = 29.62 (t), 36.74 (t), 55.95 (q), 56.22 (q), 60.97 (q), 61.01 (q), 62.87 (d), 107.08 (d), 111.64 (d), 124.74 (s), 132.48 (d), 133.91 (s), 134.82 (s), 134.97 (d), 141.30 (s), 147.25 (s), 150.67 (s), 153.55 (s), 164.00 (s), 179.17 (s). **MS** (EI, 70 eV): m/z (%) = 383 (13) $[\text{M}]^+$, 355 (11), 340 (100), 312 (45), 284 (86), 268 (24), 181 (34). **HRMS** (EI): calcd for: $[\text{M}]^+$ ($\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_5$): 383.1481; found: 383.148. **IR** (ATR): ν (cm^{-1}) = 2934, 2832, 2232, 2099, 1728, 1613, 1566, 1484, 1454, 1394, 1344, 1318, 1244, 1135, 1086, 1020, 907, 841, 722, 642. **Mp** 159 °C. $[\alpha]_{\text{D}}$ -265.9; $[\alpha]_{546}$ -356.3 (CHCl_3 , c 0.57, 20 °C).

(*aR,5S*)-Methyl azido-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c][7]annulene-3-carboxylate (8)

Sodium (24 mg, 1.04 mmol) was dissolved in 4 mL of dry MeOH at 0 °C (clear solution) and 200 mg (0.52 mmol) of azide **5** were added. The mixture was heated to 75 °C in an oil bath for 30 min. After cooling to room temperature the red solution was poured into water and the aqueous layer was extracted with EtOAc (3x). The combined organic solutions were washed with brine and dried over MgSO₄. After removal of all volatiles the crude product was purified by column chromatography (cy-hex/EtOAc = 6:1) to yield compound **8** (108 mg, 0.28 mmol, 54%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃): δ = 1.93-2.03 (m, 1 H, H-6), 2.16-2.27 (m, 1 H, H-5), 2.45-2.61 (m, 2 H, H-5, H-6), 3.62 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 4.45 (dd, ³J = 11.1 Hz, ³J = 6.6 Hz, 1 H, H-7), 6.58 (s, 1 H, H-4), 7.53 (d, ³J = 8.1 Hz, 1 H, H-11), 8.00 (d, ³J = 8.3 Hz, 1 H, H-10), 8.21 (s, 1 H, H-8). ¹³C NMR (75 MHz, CDCl₃): δ = 30.16 (t), 38.76 (t), 52.08 (q), 55.97 (q), 60.66 (d), 61.00 (q), 107.60 (d), 123.32 (s), 124.97 (d), 128.02 (d), 128.98 (s), 130.27 (d), 134.73 (s), 137.45 (s), 138.79 (s), 141.17 (s), 150.90 (s), 153.49 (s), 166.87 (s). MS (ESI, pos., 70 eV): m/z (%) = 406 [M + Na]⁺. HRMS (ESI): calcd for: [M + Na]⁺ (C₂₀H₂₁NaN₃O₅): 406.1379; found: 406.138. IR (ATR): ν (cm⁻¹) = 2936, 2860, 2826, 2246, 2226, 2099, 1715, 1594, 1550, 1483, 1433, 1399, 1343, 1399, 1293, 1229, 1193, 1088, 997, 909, 823, 726. [α]_D -57.9; [α]₅₄₆ -74.1; [α]₄₀₅ -258.0; [α]₃₆₅ -490.9 (CHCl₃, c 0.14, 20 °C).

(*aR,7S*)-7-Acetylamino-10-hydroxy-1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]heptalene-9-one (2)⁷

A solution of colchicine (**1**) (520 mg, 1.30 mmol) in 5 mL of acetic acid was treated with 30 mL of 0.1 M hydrochloric acid and the mixture was heated to 100 °C for 3 h. The solution was cooled to room temperature and adjusted to pH = 6 by portionwise addition of solid Na₂CO₃. The yellowish-green solution was extracted (3x) with CHCl₃, the organic layers were washed with brine and dried over Na₂SO₄. After evaporation of the solvent and removal of all volatiles in vacuum, 486 mg of colchicine (**2**) (1.26 mmol, 97%) were obtained as a greenish foam and directly used in the next step. ¹H NMR (300 MHz, DMSO-*d*₆): δ = 1.86 (s, 3H, H-2'), 1.90-2.20 (m, 4 H, H-5 and H-6), 3.52 (s, 3 H, OMe), 3.78 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 4.31-4.39 (m, 1 H, H-7), 6.79 (s, 1 H, H-4), 7.16 (d, ³J = 11.8 Hz, 1 H, H-11), 7.31 (s, 1 H, H-8), 7.34 (d, ³J = 11.8 Hz, 1 H, H-12) 8.62 (d, ³J = 7.3 Hz, 1 H, NH). ¹³C NMR (75 MHz, CDCl₃): δ = 29.64 (t), 37.26 (t), 52.61 (q), 55.94 (q), 61.22 (q), 61.27 (q), 107.22 (d), 119.95 (d), 122.53 (d), 125.71 (s), 134.31 (s), 136.37 (s), 141.32 (d), 150.69 (s), 151.57 (s), 153.47 (s), 170.36 (s), 175.59 (s). MS (ESI, pos., 70 eV): m/z (%) = 1181 (5), 807 (6), 532 (6), 492 (10), 424 (10) [M+K]⁺, 422 (22), 408 (96) [M+Na]⁺, 400 (33), 386 (100) [M+H]⁺, 382 (6), 344 (22), 328 (6), 327 (17) [M-NHAc]⁺, 299 (14). IR (ATR): ν (cm⁻¹) = 3254, 3045, 2993, 2934, 2849, 2830, 1706, 1654, 1605, 1592, 1540, 1485, 1449, 1400, 1358, 1345, 1319, 1273, 1227, 1191, 1133, 1090, 1042, 1006, 983,

954, 924, 918, 902, 853, 840, 797, 771, 726. **Mp** 150 °C.

(aR,5S)-N-(3-Hydroxy-2-iodo-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-5-yl)-acetamide (9)

A suspension of colchicine (**2**) (486 mg, 1.26 mmol) in 10 mL of water was cooled to 0 °C and NaOH (504 mg, 12.6 mmol) was added followed by the dropwise addition of a solution of iodine (960 mg, 3.78 mmol) and KI (3.4 g, 20.5 mmol) in 32 mL of water. The resulting orange solution was stirred for 90 min at 0 °C and then allowed to warm to room temperature. Then SO₂ was bubbled through the reaction mixture until the brown color disappeared. After 30 min the solution was acidified with conc. hydrochloric acid (pH = 2). The yellowish solid formed was isolated by filtration, washed with water (4 mL) and dried in vacuo (60 °C) to give 567 mg of **9** (1.17 mmol, 93%). **¹H NMR** (300 MHz, DMSO-*d*₆): δ = 1.81-2.15 (m, 4 H, H-5 and H-6), 1.87 (s, 3 H, H-2'), 3.48 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 4.33-4.41 (m, 1 H, H-7), 6.76 (s, 1 H, H-4), 6.87 (s, 1 H, H-11), 7.56 (s, 1 H, H-8), 8.37 (d, ³*J* = 7.9 Hz, 1 H, NH), 10.27 (s, 1 H, OH). **¹³C NMR** (75 MHz, DMSO-*d*₆): δ = 22.51 (q), 29.87 (t), 37.78 (t), 48.13 (d), 55.72 (q), 60.41 (q), 81.29 (s), 107.98 (d), 109.96 (d), 123.14 (s), 126.49 (s), 134.65 (s), 139.06 (d), 140.41 (s), 142.30 (s), 150.06 (s), 152.10 (s), 155.52 (s), 168.20 (s). **MS** (ESI, pos., 70 eV): *m/z* (%) = 1005 (3) [M₂+K]⁺, 1004 (5), 1003 (23), 987 (31), 965 (3), 879 (4), 878 (10), 862 (14), 847 (2), 779 (3), 664 (2), 648 (5), 636 (5), 633 (21), 632 (100), 566 (6), 551 (17), 538 (54), 524 (3), 508 (54), 507 (4), 506 [M+Na]⁺ (52), 425 (6), 368 (4). **IR** (ATR): ν (cm⁻¹) = 3254, 3058, 2986, 2932, 2849, 2830, 2745, 2614, 2248, 2117, 1703, 1649, 1594, 1537, 1478, 1452, 1433, 1402, 1371, 1348, 1322, 1289, 1276, 1257, 1238, 1218, 1191, 1156, 1135, 1100, 1087, 1048, 1019, 1003, 954, 928, 911, 888, 862, 823, 791, 758, 726. **Mp** 238 °C.

(aR,5S)-N-(3-Hydroxy-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-5-yl)acetamide (4a)

To a solution of **9** (567 mg, 1.17 mmol, 1 eq) in 11.3 mL of acetic acid was added zinc powder (1.69 g, 25.80 mmol, 22 eq) and the mixture was heated to 120 °C for 1 h. After cooling to room temperature the remaining solid was filtered off and washed with 3 mL of acetic acid. The filtrate was diluted with 14 mL of cold water and extracted with CHCl₃ (3x). The organic layers were washed with water (2x) and dried over Na₂SO₄, and the residue was purified by column chromatography (EtOAc, R_f = 0.3). After evaporation of the solvent in vacuo *N*-acetyl-colchicol (**4a**) (358 mg, 1.0 mmol, 85%) was isolated as a colorless solid. **¹H NMR** (300 MHz, DMSO-*d*₆): δ = 1.81-1.86 (m, 1 H, H-6), 1.87 (s, 3 H, H-2'), 1.99-2.18 (m, 3 H, H-5 and H-6), 3.45 (s, 3 H, OMe), 3.76 (s, 3 H, OMe), 3.81 (s, 3 H, OMe), 4.41-4.52 (m, 1 H, H-7), 6.67 (dd, ⁴*J* = 2.5 Hz, ³*J* = 8.3 Hz, 1 H, H-10), 6.74 (s, 1 H, H-4), 6.75 (d, ⁴*J* = 2.5 Hz, 1 H,

H-8), 7.11 (d, $^3J = 8.3$ Hz, 1 H, H-11), 8.33 (d, $^3J = 8.4$ Hz, 1 H, NH), 9.39 (s, 1 H, OH). ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 22.60$ (q), 30.34 (t), 38.36 (t), 48.04 (d), 55.70 (q), 60.42 (q), 107.85 (d), 110.10 (d), 112.79 (d), 124.30 (s), 124.60 (s), 130.33 (d), 134.62 (s), 140.42 (s), 141.58 (s), 150.22 (s), 151.73 (s), 156.35 (s), 168.12 (s). **GC-MS** (EI, 70 eV): m/z (%) = 498 (2), 463 (1), 442 (1), 425 (2), 403 (1), 385 (2), 357 (45) $[\text{M}]^+$, 342 (2), 326 (2), 298 (44), 283 (17), 267 (23), 240 (17), 225 (12), 207 (9), 189 (4), 168 (7), 153 (8), 134 (6), 115 (6), 99 (2), 82 (4), 59 (9), 43 (100). **HRMS** (EI, 70 eV): calcd for: $[\text{M}]^+$ ($\text{C}_{20}\text{H}_{23}\text{NO}_5$): 357.1576; found: 357.157. **IR** (ATR): ν (cm^{-1}) = 3288, 3065, 2986, 2932, 2849, 2830, 2679, 2588, 2150, 1996, 1882, 1703, 1644, 1605, 1579, 1540, 1478, 1449, 1429, 1401, 1351, 1322, 1289, 1273, 1234, 1221, 1191, 1172, 1152, 1141, 1099, 1081, 1048, 1002, 960, 948, 926, 908, 866, 830, 818, 791, 755, 729. $[\alpha]_{\text{D}}$ -55.8; $[\alpha]_{546}$ -73.0; $[\alpha]_{405}$ -243.3; $[\alpha]_{365}$ -421.3 (CHCl_3 , c 0.135, 20 °C).

(aR,5S)-5-Amino-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-3-ol-hydrochloride (10)

To a solution of *N*-acetyl-colchicol (4a) (574 mg, 1.61 mmol) in 5.5 mL of MeOH were added 5.5 mL of 0.2 M hydrochloric acid and the reaction mixture was heated to reflux for 65 hours. After cooling to RT a colorless solid was formed which was filtered off, washed with Et₂O (2x) and dried in vacuo to give the hydrochloride 10 (563 mg, 1.6 mmol, 99%). ^1H NMR (300 MHz, DMSO- d_6): $\delta = 1.96$ -2.12 (m, 2 H, H-5), 2.42-2.58 (m, 2 H, H-6), 3.52 (s, 3 H, OMe), 3.75 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 4.36-4.42 (m, 1 H, H-7), 6.80 (s, 1 H, H-4), 6.84-6.87 (m, 2 H, H-8 and H-10), 7.19 (d, $^3J = 9.0$ Hz, 1 H, H-11), 8.79 (s, 3 H, NH), 9.83 (s, 1 H, OH). ^{13}C NMR (75 MHz, DMSO- d_6): $\delta = 29.38$ (t), 36.87 (t), 50.14 (d), 55.77 (q), 60.43 (q), 60.49 (q), 108.09 (d), 110.08 (d), 113.97 (d), 123.69 (s), 124.24 (s), 131.04 (d), 133.92 (s), 135.86 (s), 140.64 (s), 150.26 (s), 152.19 (s), 156.52 (s). **MS** (ESI, pos., 70 eV): m/z (%) = 673 (2), 500 (2), 400 (2), 316 (21) $[\text{M}-\text{HCl}]^+$, 300 (19), 299 (100) $[\text{M}-\text{NH}_3\text{Cl}]^+$, 271 (5), 268 (10). **IR** (ATR): ν (cm^{-1}) = 3302, 3049, 2929, 2624, 2070, 1611, 1567, 1556, 1535, 1503, 1485, 1446, 1429, 1401, 1382, 1354, 1333, 1294, 1273, 1230, 1195, 1173, 1145, 1134, 1102, 1087, 1053, 1028, 1014, 1000, 992, 982, 943, 925, 904, 847, 819, 790. **Mp** 243 °C. $[\alpha]_{\text{D}}$ -92.2; $[\alpha]_{546}$ -121.5; $[\alpha]_{405}$ -451.6; $[\alpha]_{343}$ -820.8 (DMSO, c 1.15, 20 °C).

(aR,5S)-5-Azido-9,10,11-trimethoxy-6,7-dihydro-5H-dibenzo[a,c]cycloheptene-3-ol (11)

At first, a ca. 1.14 M solution of TfN₃ in toluene was freshly prepared from NaN₃ and Tf₂O (following the procedure described above for the synthesis of 5, however, replacing CH₂Cl₂ by toluene). Then, 2.78 mL (3.17 mmol) of this solution (TfN₃ in toluene) were added to a stirred mixture of hydrochloride 10 (200 mg, 0.57 mmol) in 0.4 mL of water, CuSO₄·5H₂O (7.4 mg, 0.03 mmol) and NaHCO₃ (201 mg,

2.39 mmol). The resulting mixture was diluted with 12.2 mL of MeOH and stirred for 2 hours at room temperature before the solvents were removed in vacuo. The crude product was purified by column chromatography (EtOAc/cy-hex = 1:4; R_f = 0.3) to give 122 mg (0.36 mmol, 63 %) of azide **11** as a brownish solid. **¹H NMR** (300 MHz, acetone- d_6): δ = 1.81-1.92 (m, 1 H, H-5), 2.14-2.24 (m, 1 H, H-6), 2.40-2.51 (m, 2 H, H-5 and H-6), 3.53 (s, 3 H, OMe), 3.77 (s, 3 H, OMe), 3.82 (s, 3 H, OMe), 4.36-4.42 (m, 1 H, H-7), 6.70 (s, 1 H, H-4), 6.81 (dd, 4J = 2.5 Hz, 3J = 8.4 Hz, 1 H, H-10), 7.00 (d, 4J = 2.5 Hz, 1 H, H-8), 7.25 (d, 3J = 8.4 Hz, 1 H, H-11). **¹³C NMR** (75 MHz, acetone- d_6): δ = 31.78 (t), 40.41 (t), 57.19 (q), 61.84 (q), 61.89 (q), 62.72 (d), 109.72 (d), 112.04 (d), 115.48 (d), 126.06 (s), 126.93 (s), 133.12 (d), 136.35 (s), 140.47 (s), 143.08 (s), 152.53 (s), 154.47 (s), 158.40 (s). **GC-MS** (EI, 70 eV): m/z (%) = 313 (100) $[M-N_2]^+$, 298 (6), 282 (8), 267 (7), 240 (6), 225 (6), 199 (3), 184 (5), 154 (4), 128 (6), 102 (2), 78 (3), 57 (3), 41 (4). **HRMS** (EI, 70 eV): calcd for: $[M-N_2]^+$ ($C_{18}H_{19}N_3O_4$): 313.1314; found: 313.132. **IR** (ATR): ν (cm^{-1}) = 3234, 3056, 3000, 2936, 2858, 2829, 2645, 2226, 2099, 1684, 1606, 1592, 1578, 1482, 1450, 1429, 1382, 1347, 1322, 1290, 1269, 1230, 1187, 1152, 1141, 1106, 1088, 1046, 996, 950, 932, 914, 868, 815, 790, 773, 758, 734, 702, 670, 634. **Mp** 114 °C. $[\alpha]_D$ -63.8; $[\alpha]_{546}$ -82.3; $[\alpha]_{405}$ -245.9; $[\alpha]_{365}$ -417.2 (MeOH, c 0.75, 20 °C).

General procedure for the [3+2] cycloaddition:

In a microwave vial 50 mg (130 μ mol, 1 eq.) of azide **5** (or the allo-congeners **8** or **11**, respectively) were dissolved in 0.25 mL of *t*-BuOH. To this solution 0.25 mL of water were added followed by the addition of 130 μ mol of the corresponding alkyne (1 eq.). Then 10 μ L (1 mol%) of a catalyst solution (prepared from 32.4 mg of $CuSO_4 \cdot H_2O$ in 1 mL of water) and 2.6 mg of sodium ascorbate (13 μ mol, 10 mol %) were added. The microwave vial was sealed and placed in a microwave reactor and heated to 85 °C for 20 min (300 W). After cooling to room temperature the reaction mixture was poured into water, followed by extraction of the aqueous phase with EtOAc (4x), washing the combined organic layers with brine and by drying over $MgSO_4$. The crude product (triazole) was purified by column chromatography. (For yield see Figure 2).

Triazole **12** (derived from azide **5** and propargylic alcohol)

¹H NMR (300 MHz, $CDCl_3$): δ = 7.69 (s, 1 H, H-5'), 7.26 (d, 1 H, d, 3J = 11 Hz, H-12), 6.79 (d, 1 H, 3J = 11 Hz, H-11), 6.57 (s, 1 H, H-8), 6.43 (s, 1 H, H-4), 5.39 (dd, 1 H, 3J = 11.8 Hz, 3J = 5.2 Hz, H-7), 4.75 (s, 2 H, CH_2OH), 3.93 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 2.76 – 2.68 (m, 2 H, H-5), 2.58 – 2.52 (m, 2 H, H-6). **¹³C NMR** (75 MHz, $CDCl_3$): δ = 178.80 (s), 164.18 (s), 153.92 (s), 150.94 (s), 148.31 (s), 147.85 (s), 141.62 (s), 135.54 (d), 134.57 (s), 133.51 (s), 131.65 (d),

124.81 (s), 122.26 (d), 112.03 (d), 107.38 (d), 62.62 (d), 61.16 (q, 2C), 56.59 (t), 56.37 (q), 56.09 (q), 35.32 (t), 29.64 (t). **MS** (ESI, pos., 70 eV): m/z (%) = 439 (88) $[M]^+$, 424 (16), 340 (17), 324 (78), 312 (100), 297 (70), 281 (60), 267 (38), 254 (38), 239 (37), 224 (30), 211 (36), 195 (37), 181 (54). **HRMS** (ESI): calcd for: $[M]^+$ ($C_{23}H_{25}N_3O_6$): 439.1743; found: 439.175. **IR** (ATR) ν (cm^{-1}): 3366, 2986, 2933, 2833, 1613, 1583, 1560, 1483, 1456, 1396, 1346, 1320, 1252, 1136, 1093, 1016, 743. **Mp** 150 °C. $[\alpha]_D -121.6$; $[\alpha]_{546} -174.4$ ($CHCl_3$, c 0.502, 20 °C).

Triazole 13 (derived from azide **5** and propargyl oleate)

1H NMR (500 MHz, $CDCl_3$): δ = 7.62 (s, 1 H, H-5'), 7.25 (d, 1 H, $^3J = 11.0$ Hz, H-12), 6.77 (d, 1 H, $^3J = 11.0$ Hz, H-11), 6.55 (s, 1 H, s, H-8), 6.46 (s, 1 H, s, H-4), 5.39 – 5.29 (m, 3 H, H-7, $CH=CH$), 5.20 (s, 2 H, CH_2O), 3.94 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 3.87 (s, 3 H, OMe), 3.73 (s, 3 H, OMe), 2.78 – 2.68 (m, 2 H, H-5), 2.60 – 2.49 (m, 2 H, H-6), 2.27 (t, 2 H, $^3J = 7.6$ Hz), 1.97 – 1.94 (m, 4 H, $CH_2CH=CH$), 1.60 – 1.52 (m, 2 H), 1.33 – 1.17 (m, 20 H, CH_2), 0.83 (t, 3 H, $^3J = 6.7$ Hz, CH_2CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 178.75 (s), 173.70 (s), 164.20 (s), 153.88 (s), 150.92 (s), 147.41 (s), 143.10 (s), 141.58 (s), 135.37(d), 134.30 (s), 133.44 (s), 131.76 (d), 129.89 (d), 129.66 (d), 124.79 (s), 124.22 (d), 111.69 (d), 107.26 (d), 62.63 (d), 61.24 (q), 61.13 (q), 57.36 (t), 56.35 (q), 56.05 (q), 35.30 (t), 34.03 (t), 31.82 (t), 29.68 (t, 2C), 29.61 (t), 29.44 (t), 29.24 (t, 2C), 29.07 (t), 29.02 (t), 29.00 (t), 27.13 (t), 27.09 (t), 24.71 (t), 22.60 (t), 14.06 (q). **MS** (EI, 70 eV) m/z (%): 704 (1) $[M]^+$, 589 (1), 342 (98), 314 (100), 297 (23), 282 (35), 267 (17), 251 (12), 239 (12), 224 (9), 211 (9), 195 (8), 181 (15). **HRMS** (EI): calcd for $[M]^+$ ($C_{41}H_{57}N_3O_7$): 703.4197; found: 703.421. **IR** (ATR) ν (cm^{-1}): 2997, 2922, 2850, 1735, 1618, 1585, 1486, 1459, 1398, 1348, 1321, 1251, 1138, 1095, 1019, 842 cm^{-1} . $[\alpha]_D -76.1$; $[\alpha]_{546} -107.4$ ($CHCl_3$, c 0.602, 20 °C).

Triazole 14 (derived from azide **5** and propargyl palmitate)

1H NMR (300 MHz, $CDCl_3$): δ = 7.61 (s, 1 H, H-5'), 7.24 (d, 1 H, $^3J = 10.7$ Hz, H-12), 6.76 (d, 1 H, $^3J = 10.7$ Hz, H-11), 6.54 (s, 1 H, H-8), 6.44 (s, 1 H, H-4), 5.33 (dd, 1 H, $^3J = 11.8$ Hz, $^3J = 5.2$ Hz, H-7), 5.17 (s, 2 H, CH_2O), 3.93 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 3.86 (s, 3 H, OMe), 3.72 (s, 3 H, OMe), 2.84 – 2.64 (m, 2 H, H-5), 2.59 – 2.42 (m, 2 H, H-6), 2.26 (t, 2 H, $^3J = 7.6$ Hz, $C(O)CH_2$), 1.63 – 1.45 (m, 2 H, $C(O)CH_2CH_2$), 1.26 – 1.12 (m, 24 H, CH_2), 0.82 (t, 3 H, $^3J = 6.6$ Hz, CH_2CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 178.72 (s), 173.67 (s), 164.18 (s), 153.87(s), 150.90 (s), 147.38 (s), 143.10 (s), 141.59 (s), 135.32 (d), 134.28 (s), 133.42 (s), 131.74 (d), 124.78 (s), 124.18 (d), 111.67 (d), 107.28 (d), 62.62 (d), 61.19 (q), 61.08 (q), 57.34 (t), 56.32 (q), 56.03 (q), 35.28 (t), 34.01 (t), 31.81 (t), 29.57 (t, 7C), 29.34 (t), 29.24 (t), 29.12 (t), 29.00 (t), 24.69 (t), 22.57 (t), 14.01 (q). **MS** (EI, 70 eV) m/z (%): 678 (23) $[M]^+$, 562 (6), 394 (10), 341 (29), 312 (100), 297 (52), 282 (58), 267 (29), 251 (23), 239 (26), 224 (16), 211 (16),

195 (16), 181 (26). **HRMS** (EI): calcd for $[M]^+$ ($C_{39}H_{55}N_3O_7$): 677.4039; found: 677.404. **IR** (ATR) ν (cm^{-1}): 2921, 2850, 1735, 1617, 1585, 1486, 1460, 1398, 1348, 1321, 1251, 1138, 1095, 1019, 842. **Mp** 50 °C. $[\alpha]_D -84.0$; $[\alpha]_{546} -119.5$ ($CHCl_3$, c 0.535, 20 °C).

Triazole 15 (derived from azide **8** and propargylic alcohol)

1H NMR (300 MHz, $CDCl_3$): δ = 7.98 (dd, 1 H, $^3J = 8.2$ Hz, $^4J = 1.6$ Hz, H-10), 7.57 (d, 1 H, $^3J = 8.2$ Hz, H-11), 7.18 (d, 1 H, $^4J = 1.6$ Hz, H-8), 6.62 (s, 1 H, s, H-4), 5.49 (dd, 1 H, $^3J = 12.6$ Hz, $^3J = 6.0$ Hz, H-7), 4.79 (s, 2 H, CH_2OH), 3.89 (s, 6 H, OMe), 3.79 (s, 3 H, OMe), 3.68 (s, 3 H, OMe), 2.94 – 2.87 (m, 1 H, H-6a), 2.67 – 2.60 (m, 2 H, H-5), 2.44 – 2.37 (m, 1 H, H-6b). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 166.95 (s), 154.23 (s), 151.45 (s), 148.20 (s), 141.73 (s), 138.96 (s), 137.69 (s), 134.71 (s), 130.85 (d), 129.57 (s), 128.78 (d), 124.56 (d), 123.49 (s), 122.77 (d), 108.16 (d), 61.55 (d), 61.43 (q), 61.08 (q), 56.93 (t), 56.45 (q), 52.53 (t), 38.20 (q), 30.60 (t). **MS** (EI, 70 eV) m/z (%): 439 (42) $[M]^+$, 352 (21), 340 (100), 325 (36), 309 (45), 297 (19), 282 (23), 267 (18), 251 (24), 239 (14), 224 (16), 207 (16), 193 (15), 181 (31). **HRMS** (EI): calcd for $[M]^+$ ($C_{23}H_{25}N_3O_6$): 439.1743; found: 439.173. **IR** (ATR) ν (cm^{-1}): 3355, 2937, 2860, 1717, 1595, 1484, 1455, 1434, 1401, 1348, 1323, 1296, 1237, 1194, 1146, 1106, 1086, 1046, 1006, 823, 749. **Mp** 97 °C. $[\alpha]_D -117.3$; $[\alpha]_{546} -156.2$ ($CHCl_3$, c 0.4, 20 °C).

Triazole 16 (derived from azide **8** and propargyl oleate)

1H NMR (300 MHz, $CDCl_3$): δ = 8.00 (dd, 1 H, $^3J = 8.1$ Hz, $^4J = 1.6$ Hz, H-10), 7.66 (s, 1 H, H-5'), 7.57 (d, 1 H, $^3J = 8.1$ Hz, H-11), 7.19 (d, 1 H, $^4J = 1.6$ Hz, H-8), 6.62 (s, 1 H, H-4), 5.48 (dd, 1 H, $^3J = 12.4$ Hz, $^3J = 5.9$ Hz, H-7), 5.33 – 5.26 (m, 2 H, $CH=CH$), 5.24 (s, 2 H, CH_2O), 3.90 (s, 6 H, OMe), 3.81 (s, 3 H, OMe), 3.70 (s, 3 H, OMe), 3.01 – 2.90 (m, 1 H, H-6a), 2.69 – 2.55 (m, 2 H, H-5), 2.45 – 2.31 (m, 1 H, H-6b), 2.29 (t, 2 H, $^3J = 7.6$ Hz, $C(O)CH_2$), 1.99 – 1.90 (m, 4 H, $CH_2CH=CH$), 1.68 – 1.46 (m, 2 H, $C(O)CH_2CH_2$), 1.33 – 1.15 (m, 20 H, CH_2), 0.84 (t, 3 H, $^3J = 6.7$ Hz, CH_2CH_3). **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 173.65 (s), 166.42 (s), 153.86 (s), 151.07 (s), 143.02 (s), 141.36 (s), 138.51 (s), 137.16 (s), 134.31 (d), 130.46 (d), 129.93 (d), 129.64 (d), 129.29 (s), 128.45 (d), 124.43 (d), 124.19 (d), 123.11 (s), 107.73 (d), 61.17 (q), 61.02 (q), 60.75 (q), 57.50 (t), 56.05 (q), 52.07 (q), 37.81 (t), 34.07 (t), 31.83 (t), 30.21 (t), 29.69 (t), 29.62 (t), 29.45 (t), 29.25 (t), 29.07 (t), 29.03 (t), 27.14 (t), 27.10 (t), 24.74 (t), 22.61 (t), 14.05 (t). **MS** (EI, 70 eV) m/z (%): 704 (2) $[M]^+$, 617 (1), 394 (5), 362 (17), 341 (100), 313 (15), 309 (27), 297 (7), 282 (15), 266 (12), 251 (15), 235 (7), 224 (6), 208 (6), 193 (5), 181 (8). **HRMS** (EI): calcd for $[M]^+$ ($C_{41}H_{57}N_3O_7$): 703.4196; found: 703.421. **IR** (ATR) ν (cm^{-1}): 2997, 2922, 2851, 1723, 1595, 1484, 1456, 1434, 1400, 1348, 1324, 1293, 1236, 1194, 1146, 1115, 1087, 1049, 1007, 823, 771. $[\alpha]_D -73.4$; $[\alpha]_{546} -98.2$ ($CHCl_3$, c 0.504, 20 °C).

Triazole 17 (derived from azide **8** and propargyl palmitate)

¹H NMR (300 MHz, CDCl₃): δ = 8.00 (dd, 1 H, ³J = 8.1 Hz, ⁴J = 1.6 Hz, H-10), 7.66 (s, 1 H, H-5'), 7.57 (d, 1 H, ³J = 8.1 Hz, H-11), 7.19 (d, 1 H, ⁴J = 1.6 Hz, H-8), 6.62 (s, 1 H, H-4), 5.48 (dd, 1 H, ³J = 12.4 Hz, ³J = 5.9 Hz, H-7), 5.24 (s, 2 H, CH₂O), 3.90 (s, 6 H, OMe), 3.81 (s, 3 H, OMe), 3.71 (s, 3 H, OMe), 3.02 – 2.90 (m, 1 H, H-6a), 2.72 – 2.60 (m, 2 H, H-5), 2.48 – 2.34 (m, 1 H, H-6b), 2.29 (t, 2 H, ³J = 7.6 Hz, C(O)CH₂), 1.62 – 1.52 (m, 2 H, C(O)CH₂CH₂), 1.30 – 1.18 (m, 24 H, CH₂), 0.84 (t, 3 H, ³J = 6.7 Hz, CH₂CH₃). **¹³C NMR** (75 MHz, CDCl₃): δ = 173.68 (s), 166.42 (s), 153.86 (s), 151.08 (s), 143.04 (s), 141.37 (s), 138.51 (s), 137.17 (s), 134.31 (s), 130.46 (d), 129.30 (s), 128.46 (d), 124.42 (d), 124.20 (d), 123.12 (s), 107.73 (d), 61.18 (d), 61.02 (q), 60.75 (q), 57.51 (t), 56.06 (q), 52.08 (q), 37.82 (t), 34.09 (t), 31.86 (t), 30.22 (t), 29.61 (t, 6C), 29.39 (t), 29.30 (t), 29.18 (t), 29.07 (t), 24.76 (t), 22.63 (t), 14.06 (q). **MS** (EI, 70 eV) *m/z* (%): 678 (8) [M]⁺, 591 (1), 394 (5), 366 (8), 350 (6), 340 (100), 325 (21), 309 (28), 297 (9), 282 (15), 267 (13), 251 (14), 239 (8), 224 (7), 208 (6), 195 (5), 181 (9). **HRMS** (EI): calcd for [M]⁺ (C₃₉H₅₅N₃O₇): 677.4039; found: 677.404. **IR** (ATR) *v* (cm⁻¹): 2920, 2849, 1722, 1595, 1484, 1455, 1434, 1401, 1348, 1324, 1293, 1236, 1194, 1147, 1115, 1088, 1049, 1007, 823, 771. [α]_D -73.3; [α]₅₄₆ -98.4 (CHCl₃, c 0.425, 20 °C).

Triazole 18 (derived from azide **11** and propargyl ferrocenecarboxylate)

¹H NMR (300 MHz, CDCl₃): δ = 1.50-1.86 (m, 1 H, H-5), 2.50-2.64 (m, 3 H, H-5 and H-6), 3.75 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 4.08 (s, 5 H, H-Cp), 4.38 (s, 2 H, H-4'), 4.77 (s, 2 H, H-3'), 5.26 (q, ⁴J = 15.3 Hz, 2 H, H-3'), 5.37-5.42 (m, 1 H, H-7), 6.16 (d, ⁴J = 2.2 Hz, 1 H, H-8), 6.62 (s, 1 H, H-4), 6.91 (dd, ⁴J = 2.2 Hz, ³J = 8.4 Hz, 1 H, H-10), 7.41 (d, ³J = 8.4 Hz, 1 H, H-11), 7.68 (s, 1 H, H-1'), 7.97 (s, 1 H, OH). **¹³C NMR** (75 MHz, CDCl₃): δ = 30.47 (t), 37.67 (t), 56.06 (q), 56.87 (t), 61.04 (q), 61.53 (q), 69.80 (d), 70.27 (d), 70.29 (d), 71.64 (d), 107.63 (d), 109.98 (d), 114.98 (d), 124.13 (s), 124.89 (s), 125.30 (d), 131.66 (d), 134.30 (s), 137.97 (s), 141.29 (s), 142.75 (s), 151.00 (s), 152.75 (s), 156.56 (s), 171.76 (s). **MS** (ESI, pos., 70 eV): *m/z* (%) = 633 (17), 632 (53) [M+Na]⁺, 610 (61) [M+H]⁺, 532 (100), 533 (25), 498 (10), 400 (17), 382 (73), 352 (49), 324 (25), 299 (33), 213 (6), 185 (42), 143 (13), 65 (6). **HRMS** (ESI): calcd for: [M]⁺ (C₃₂H₃₁FeN₃O₆): 609.1562, found: 609.156. **IR** (ATR): *v* (cm⁻¹) = 3142, 3052, 2996, 2930, 2850, 2724, 2682, 2592, 2459, 2243, 1902, 1709, 1609, 1594, 1580, 1484, 1456, 1431, 1403, 1372, 1347, 1324, 1234, 1191, 1140, 1125, 1105, 1087, 1049, 1025, 1003, 951, 935, 914, 865, 822, 792, 753, 730, 664, 643, 636. **Mp.** 201 °C. [α]_D -51.3; [α]₅₄₆ -74.7 (CHCl₃, c 0.79, 20 °C).

Triazole 19 (derived from azide **11** and propargyl dodecanoate)

¹H NMR (300 MHz, CDCl₃): δ = 0.87 (t, ³J = 6.3 Hz, 3 H, H-12'), 1.23 (s, 16 H, H-4'-H-11'), 1.57

(t, $^3J = 7.1$ Hz, 2 H, H-3''), 2.28 (t, $^3J = 7.5$ Hz, 2 H, H-2''), 2.45-2.65 (m, 3 H, H-5 and H-6), 3.08-3.18 (m, 1 H, H-6), 3.76 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 3.93 (s, 3 H, OMe), 5.12 (q, $J = 6.5$ Hz, 2 H, H-3'), 5.33-5.39 (m, 1 H, H-7), 6.06 (d, $^4J = 2.4$ Hz, 1 H, H-8), 6.63 (s, 1 H, H-4), 6.89 (dd, $^4J = 2.4$ Hz, $^3J = 8.4$ Hz, 1 H, H-10), 7.40 (d, $^3J = 8.4$ Hz, 1 H, H-11), 7.57 (s, 1 H, H-1'), 7.84 (s, 1 H, NH). **^{13}C NMR** (75 MHz, CDCl_3): $\delta = 14.15$ (q), 22.71 (t), 24.80 (t), 29.13 (t), 29.26 (t), 29.36 (t), 29.47 (t), 29.62 (t), 30.50 (t), 31.93 (t), 34.05 (t), 37.47 (t), 56.11 (q), 57.15 (t), 61.07 (q), 61.60 (q), 107.67 (d), 109.97 (d), 115.01 (d), 124.15 (s), 124.61 (d), 131.68 (d), 134.41 (s), 138.13 (s), 141.33 (s), 142.69 (s), 151.03 (s), 152.83 (s), 156.61 (s), 173.73 (s). **MS** (ESI, pos., 70 eV): m/z (%) = 1184 (1), 1183 (2), 1182 (2) $[\text{M}_2+\text{Na}]^+$, 1180 (1), 900 (1), 897 (2), 898 (2), 890 (1), 889 (2), 881 (1), 882 (1), 619 (14), 618 (35) $[\text{M}+\text{K}]^+$, 603 (37), 602 (100) $[\text{M}+\text{Na}]^+$, 580 (6) $[\text{M}+\text{H}]^+$, 449 (6), 346 (7), 244 (1), 243 (7), 241 (4). **HRMS** (ESI, pos., 70 eV): calcd for: $[\text{M}+\text{Na}]^+$ ($\text{C}_{33}\text{H}_{45}\text{N}_3\text{O}_6\text{Na}$): 602.3206, found: 602.320. **IR** (ATR): ν (cm^{-1}) = 3143, 2920, 2849, 2357, 2338, 1735, 1697, 1681, 1648, 1607, 1595, 1579, 1566, 1556, 1537, 1502, 1483, 1454, 1429, 1400, 1371, 1346, 1320, 1292, 1272, 1234, 1193, 1170, 1154, 1142, 1107, 1084, 1049, 1005, 919, 864, 820, 764. **Mp** 66 °C. $[\alpha]_{\text{D}}$ -11.0; $[\alpha]_{546}$ -16.4; $[\alpha]_{405}$ -91.7; $[\alpha]_{365}$ -182.8 (MeOH, c 0.50, 20 °C).

Triazole 20 (derived from azide **11** and propargyl 2-acetoxybenzoate)

^1H NMR (300 MHz, CDCl_3): $\delta = 2.18$ (s, 3 H, H-9''), 2.47-2.74 (m, 4 H, H-5 and H-6), 3.62 (s, 3 H, OMe), 3.85 (s, 2 x 3 H, OMe), 5.33 (d, $^3J = 12.3$ Hz, 1 H, H-7), 5.49-5.57 (m, 2 H, H-3'), 5.65 (d, $^4J = 2.4$ Hz, 1 H, H-8), 6.56 (s, 1 H, H-4), 6.75 (dd, $^4J = 2.4$ Hz, $^3J = 8.4$ Hz, 1 H, H-10), 7.01 (s, 1 H, H-6''), 7.30 (t, $^3J = 8.4$ Hz, 2 H, H-4'' and H-11), 7.53 (dt, $^4J = 1.6$ Hz, $^4J = 7.8$ Hz, 1 H, H-5''), 7.80 (s, 1 H, H-1'), 8.01 (dd, $^4J = 1.6$ Hz, $^4J = 7.8$ Hz, 1 H, H-3''). **^{13}C NMR** (75 MHz, CDCl_3): $\delta = 21.12$ (q), 30.38 (t), 37.80 (t), 56.09 (q), 58.12 (t), 60.99 (q), 61.08 (q), 62.31 (d), 107.59 (d), 109.21 (d), 114.67 (d), 123.38 (d), 125.10 (d), 126.53 (d), 126.82 (s) 131.86 (d), 132.23 (d), 133.99 (s), 134.32 (d), 137.90 (s), 141.82 (s), 142.32 (s), 151.14 (s), 152.74 (s), 156.30 (s), 164.79 (s), 170.92 (s). **MS** (ESI, pos., 70 eV): m/z (%) = 599 (16), 598 (39) $[\text{M}+\text{K}]^+$, 583 (27), 582 (100) $[\text{M}+\text{Na}]^+$, 560 (35), 299 (10). **HRMS** (ESI, pos., 70 eV): calcd for: $[\text{M}+\text{Na}]^+$ ($\text{C}_{30}\text{H}_{29}\text{N}_3\text{O}_8\text{Na}$): 582.1852, found: 582.185. **IR** (ATR): ν (cm^{-1}) = 3381, 2945, 2915, 2847, 1764, 1705, 1649, 1642, 1633, 1606, 1579, 1537, 1484, 1451, 1429, 1403, 1366, 1324, 1289, 1269, 1247, 1231, 1194, 1154, 1139, 1107, 1086, 1049, 1040, 1007, 950, 931, 917, 861, 820, 791. $[\alpha]_{405}$ -35.5; $[\alpha]_{365}$ -81.7; $[\alpha]_{334}$ -178.2 (CHCl_3 , c 1.0, 20 °C).

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 21. In contrast to a misleading statement in the literature (Besong, D. Billen, I. Dager, P. Kocienski, E. Sliwinski, L. R. Tai, and F. T. Boyle, *Tetrahedron*, 2008, **64**, 4700) the preparation of **9** through oxidative degradation under the Windaus conditions only works with colchicine (**2**) as a substrate but not with colchicine (**1**) itself.
 22. The mechanism originally proposed by Fernholz (ref. 8) is not compatible with our modern understanding of organic reactions, but even in the famous textbook of L. Fieser and M. Fieser (*Organische Chemie*, 2. Ed., Verlag Chemie, 1968) the colchicine-allocholchicine rearrangement is (erroneously) classified as a benzilic acid rearrangement.
 23. Long before the theory of electrocyclic reactions was introduced by Woodward and Hoffmann (giving the cycloheptatriene-norcaradiene interconversion as an example) the fragmentation of a norcaradiene intermediate related to **22** was suggested by W. Leimgruber, *Dissertation* ETH Zürich, 1959, footnote on p. 33. We are very grateful to Prof. A. Eschenmoser for bringing this to our attention. Also, in their seminal paper on tropolone (ref. 20), Doering and Knox already considered norcaradienes (drawn as resonance structures) participating in such rearrangements.