Pergamon

Tetrahedron 56 (2000) 1917–1922

TETRAHEDRON

Synthesis of 1-Oxaazulan-2-ones and Furanotropones from Troponoids: a Reexamination and Extension to Colchicinoids

Marino Cavazza,[a] Graziano Guella[b] and Francesco Pietra[c,*]

[a]*Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, I-56100, Pisa, Italy*
[b]*Laboratorio di Chimica Bioorganica, Università di Trento, I-38050 Povo-Trento, Italy*
[c]*Centro Linceo Interdisciplinare B. Segre, via della Lungara 10, I-00165 Roma, Italy*

Received 5 August 1999; revised 24 January 2000; accepted 3 February 2000

Abstract—Reactions of [3,5,7-$^2H_3$]-2-tosyloxytropone (**1b**) in DMSO with enolates that, like sodium ethyl acetoacetate or sodium diethyl malonate, bear a leaving group, occur at C-7, followed by either sequential protonation at C-2, 1,6-elimination, and intramolecular heterocyclization (to give 1-oxaazulan-2-ones), or sequential sulfinate loss and intramolecular heterocyclization (to give furanotropones). The latter is the exclusive route with enolates that, like sodium acetylacetonate, do not bear a leaving group. 9-Tosyloxyisocolchicide (**15**) behaves like 2-tosyloxytropone, giving the product **16** of C-11 attack, whereas 10-tosyloxycolchicide (**17**) resists attack at C-8 and only a very slow nucleophilic attack at C-10 by the enolate to give **18** is observed. Hydroxylic solvents do not allow any of these processes.

Simple troponoids have long found use as synthons,[1] while their condensation products with enolates that bear a leaving group are a recent addition to this methodology, specifically adapted to the synthesis of guaianolides and octalactins.[2] The basic knowledge of these reactions of troponoids with enolates dates from the early 1970s,[3] before which no detailed study of the mechanism of the reactions of troponoids with *N*- and *O*-nucleophiles had been carried out.[4] In addition, no extension of these reactions to colchicinoids has appeared. The usefulness of these reactions in synthesis could be amplified by a clarification of both these aspects, which was the aim of this study.

Troponoid Series

The reactivity of 2-tosyloxytropone (**1a**) toward sodium ethyl acetoacetate in DMSO was first studied, isolating the 1-oxaazulan-2-one **2a** and the furanotropone **3a**, both in low yields (Scheme 1). Detailed NMR and MS analysis (Experimental) support structure **3a** and confirm the assignment of **2a**.[3] Deuterium labeling of 2-tosyloxytropone (**1b**) proves that these reactions occur by C-7 attack of the enolate on the troponoid, substantiating an early hypothesis from non-labeled material.[3]

Using diethyl malonate as an enolate we obtained the corresponding 1-oxaazulan-2-one **5** in fair yield as a single product (Scheme 1). Detailed NMR and MS data (Experimental) confirm the structure.[3]

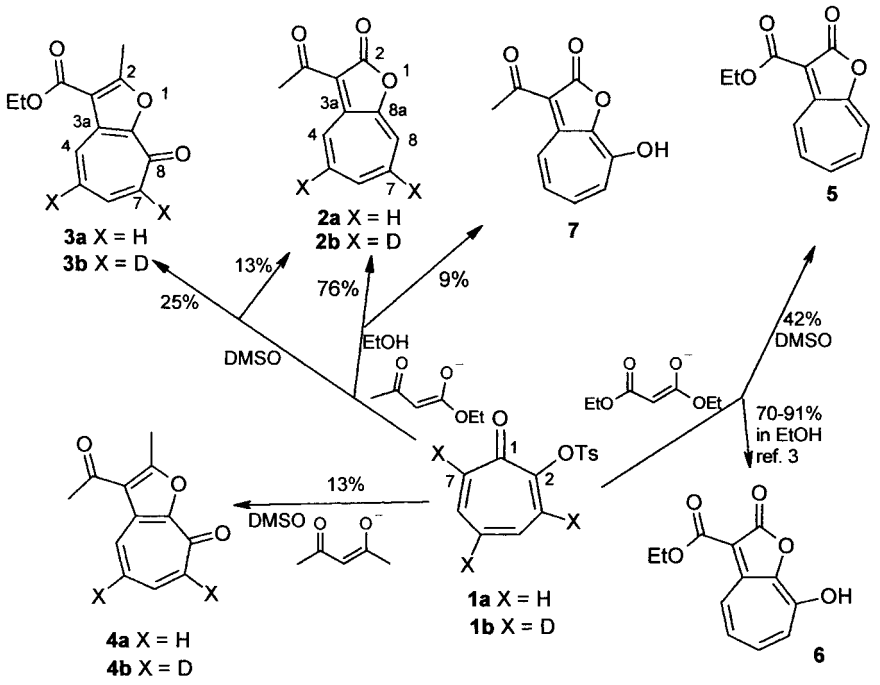
It should be noted that in absolute EtOH the reactions reportedly[3] took a different course. Thus, **1a** and diethyl malonate led to only traces of **5**, while the major product was 8-hydroxy-3-carboethoxy-1-oxa-azulan-2-one (**6**).[3] With ethyl acetoacetate, 8-hydroxy-3-acetyl-1-oxaazulan-2-one (**7**) was a by product (9%) in place of **3a**, while the major product (76%) was **2a**.[3]

Enolates that lack a leaving group had not been investigated before in this context. Using acetyl acetonate in DMSO, we have obtained furanotropone **4a** in low yield from **1a**. Deuterium labeling shows that C-7 is attacked by the enolate to give **4b**. Both structures are fully supported by NMR and MS data (Experimental).

These observations can be fitted into the general reactivity Scheme 2. As for the reaction by ethyl acetoacetate, it can be conceived that intermediate **8**, deriving from attack by the enolate at C-7 of the substrate, can take either one of two main pathways. Pathway **a** involves protonation at C-2 to give intermediate **9**, followed by the loss of toluensulfonic acid (or deuterotoluensulfonic acid) to give intermediate **10** or **11**. The latter only is stereochemically prone to intramolecular condensation to give **2a** (or **2b**). Pathway **b** involves loss of sulfinate, followed by intramolecular condensation at the acetyl moiety and loss of water to give **3a** (or **3b**) via **13**. No products from the putative intermediate **14**, which could result from the alternative

Keywords: alkaloids; colchicinoids; furans; cyclisation; enolates; lactonisation; regioselection; solvents and solvent effect.
* Corresponding author. Tel.: +39-0583-490282; fax: +39-0583-490282; e-mail: fpietra@discat.unipi.it

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00106-X



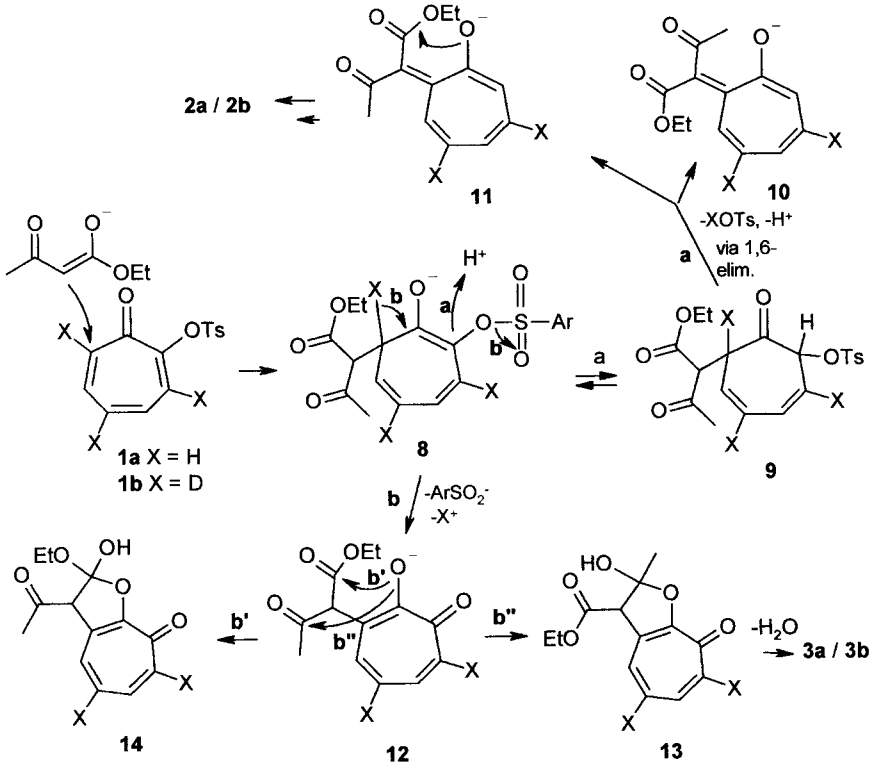
Scheme 1. Reactions of 2-tosyloxytropone (**1a**) or [3,5,7-$^2H_3$]-2-tosyloxytropone (**1b**) with sodium acetyl acetonate, ethyl acetoacetate, or diethyl malonate in DMSO, unless otherwise stated.

intramolecular condensation at the ester group, were noticed. With diethyl malonate, unproductive intermediates of type **10** are not formed, so a high yield of **5** is obtained.

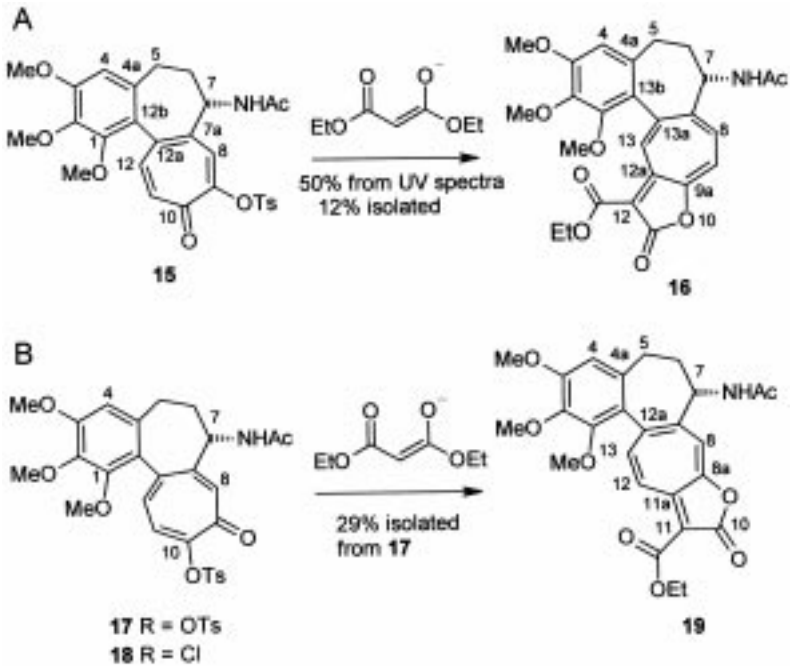
Finally, with acetyl acetonate the route **a** cannot take place and only route **b** occurs, leading to **4a** (or **4b**).

Colchicinoid Series

In view of the better yields of condensation products obtained for troponoids with diethyl malonate, the latter was chosen to explore the behavior of colchicinoids. 9-Tosyloxyisocolchicide (**15**) behaves like 2-tosyloxytropone, giving a single product, **16**, which can be imagined to result



Scheme 2. Proposed mechanism for the reaction of 2-tosyloxytropone (**1a**) with sodium ethyl acetoacetate.



Scheme 3. Reactions of 9-tosyloxyisocolchicide (**15**) or 10-tosyloxycolchicide (**17**) or 10-chlorocolchicine (**18**) with sodium diethyl malonate in DMSO.

from C-11 attack by the enolate (Scheme 3). Structure **16** is fully supported by MS and NMR data (Experimental), the latter perfectly fitting deductions from the energy-minimized structure (Fig. 1).[5] Difficulties in small-scale reactions in recovering products that are strongly adsorbed by the chromatographic support, and formation of colchiceine, account for the low yield of isolated **16**.

10-Tosyloxycolchicide (**17**) or, with better yields, 10-chlorocolchicide (**18**), also gave a single product, **19**, albeit in sluggish reactions where much of unreacted **17** or **18** were recovered (Scheme 3). Structure **19**, which is fully supported by NMR and MS data (Experimental), implies attack by the enolate at C-10, in contrast with all the observations above for either the troponoids or colchicinoid **15**. Lack of formation of products from attack at C-8 by carbon nucleophiles with 1-tosyloxycolchicide finds analogy in the behavior of this substrate toward either amines[6] or amidines.[7] Such an inversion of reactivity may tentatively be attributed to steric hindrance in the tetrahedral intermediate for attack at C-8, which overcomes an electronic preference.[8] We have no evidence for radical anion routes.

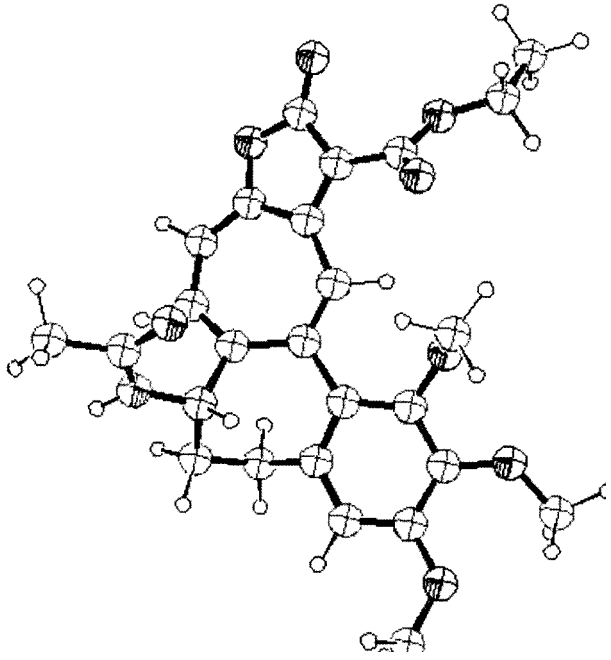


Figure 1. Strain-energy minimized conformation for compound **16**.

Perspective

This work represents a rationalization, on the basis of novel observations as to solvent directivity of the reaction course, for annelation reactions of troponoids with enolates that carry nucleofugic groups. Although yields have not been optimized, these reactions proved applicable to isocolchicinoids and colchicinoids, annelating a butenolide ring to the cycloheptatrienone moiety, with transposition in the first case and no transposition in the second one. These tetracyclic products could hardly be obtained by current technologies. The colchicinoid framework is often endowed with powerful biological activities,[9] in particular hindering the polymerization of tubulin, where the interaction sites with colchicine are known.[10] These points of contact are altered drastically in compounds **16** and **19**, while offering new opportunities for interaction in the same critical region that warrant biological assays to be carried out.

Experimental

General

All evaporations were carried out under reduced pressure. Yields are given on reacted substrate. DMSO was dried on

3 Å molecular sieves and was stored under N_2 in Schlenk tubes. TLC: Merck Kieselgel 60 F_{254} plates. Reversed-phase HPLC: Spherisorb RP18, 8×250 mm, with 1:1 MeCN–H_2O, flux 3 mL min^{-1}. IR: Perkin–Elmer 1725X FT-IR spectrometer. UV: Perkin–Elmer Hitachi 200 spectrophotometer; λ_{max} in nm, in mol^{-1} L cm^{-1}. NMR: Varian XL-300 spectrometer (^1H 299.94 MHz, ^{13}C 75.43 MHz) operating under inverse detection, or, when indicated, Varian Gemini BB200 spectrometer (^1H 199.975 MHz and ^{13}C 50.289 MHz); δ in ppm rel. to internal Me_4Si (=0 ppm) and J in Hz; assignments from DEPT and ^1H, ^{13}C COSY. The number of protons given for each ^1H NMR signal often results from decoupling and other techniques and not from integration for non-first order spectra with protons of widely different relaxation properties. MS (EI): Kratos MS80 with home-built data system; *m*/*z* (rel.%).

General procedure for the reactions of enolates with either troponoids or colchicinoids

To a stirred suspension of MeONa (ca. 2 mmol) in dried DMSO (4 mL) at room temperature was added the enolizable reagent, in a 1.2 molar excess under N_2, followed by the troponoid or the colchicinoid (ca. 0.9 mmol), by which the mixture turned immediately to orange-red in color. The mixture was stirred for 30 min, unless otherwise stated, and then it was acidified with dilute HCl (0.5 M, 5 mL) and was extracted with $CHCl_3$ (10×3 mL). The organic phase was washed three times with H_2O (5 mL), separated, dried over Na_2SO_4, and evaporated. The residue was subjected to TLC purification with Et_2O, unless otherwise stated. No optimization of yields was performed.

Reaction of 2-tosyloxytropone (1a) with sodium ethylacetoacetate

Using MeONa (0.083 g, 1.54 mmol), ethyl acetoacetate (0.20 mL, 1.6 mmol), and **1a** (0.194 g, 0.7 mmol) in DMSO (4 mL), we obtained **2a**[3,11] (0.033 g, 0.175 mmol, 25%) as a yellow solid, mp 207–208°C, EtOH; lit.[3] 208–209°C; R_f 0.57, and **3a** (0.022 g, 0.095 mmol, 13.5%) as a colorless semi-solid, R_f 0.43.

Data of 3-acetyl-2*H*-cyclohepta[b]furan-2-one (2a). UV: λ_{max}(MeOH) nm/(log ϵ) 416 (3.9), 271 (3.8), 247. ν_{max} (Nujol) 1733, 1654, 1617, 1584, 1532, 1262 cm^{-1}. δ_H ($(CD_3)_2CO$) 9.13 (1 H, ddd, J=0.6, 1.0,11.3 Hz, 4-H), 7.91 (1 H, ddd, J=1.1, 8.9, 11.3 Hz, 5-H), 7.83 (1 H, dddd, J= 0.6, 1.1, 9.4, 10.0 Hz, 7-H), 7.78 (1 H, dd, J=1.7, 9.4 Hz, 8-H), 7.63 (1 H, dddd, J=1.0, 1.7, 8.9, 10.0 Hz, 6-H), 2.88 (3 H, s, $COCH_3$). δ_H ($CDCl_3$) 9.19 (1 H, d, 10.8 Hz, 4-H), 7.69 (1 H, dd, J=10.8, 8.9 Hz, 5-H), 7.57 (2 H, m, 7-H and 8-H), 7.42 (1 H, m, 6-H), 2.63 (3 H, s, $COCH_3$). δ_C ($CDCl_3$) 195.10 (s, *C*OCH_3), 167.53 (s, C-2), 159.12 (s, C-8a), 153.29 (s, C-3), 140.83 (d, C-5), 136.55 (d, C-7), 135.00 (d, C-6), 131.76 (d, C-4), 120.09 (d, C-8), 103.57 (s, C-3a), 30.08 (q, CO*C*H_3). *m*/*z* 188 (36, M^+), 173 (100, $[M-Me]^+$), 89 (23), 43 (23). HR-MS: M^+, found 188.0473±0.005. $C_{11}H_8O_3^+$ requires 188.0473); $[M-Me]^+$, found 173.0231±0.001. $C_{10}H_5O_3^+$ requires 173.0239).

Data of 2-methyl-3-ethoxycarbonyl-8*H*-cyclohepta[b]-furan-8-one (3a). UV λ_{max}(MeOH) nm/(log ϵ) 350, 335, 320, 310 series of sh, 297 (3.70), 258 (3.96). ν_{max} (Nujol) 1709, 1614, 1577, 1541, 1515 cm^{-1}. δ_H ($(CD_3)_2SO$) 8.20 (1 H, ddd, J=0.6, 1.0, 11.2 Hz, 4-H), 7.47 (1 H, dddd, J=0.6, 1.0, 8.6 Hz, 12.4, 6-H), 7.22 (ddd, J=0.8, 8.6, 11.2 Hz, 5-H), 7.17 (1 H, tdd, J=0.8, 1.0, 12.4 Hz, 7-H), 4.36 (2 H, q, J=7.0 Hz, CH_2CH$_3$), 2.74 (3 H, s, CH_3-C2), 1.36 (3 H, t, J=7.0 Hz, CH_2CH_3); δ_H (200 MHz, $CDCl_3$) 8.35 (1 H, d, J=11.1 Hz, 4-H), 7.34 (1 H, m, 6-H), 7.31 (1 H, m, 7-H), 7.10 (1 H, ddd, J=11.1, 8.6, 1.0 Hz, 5-H), 4.42 (2 H, q, J=7.0 Hz, CH_2CH$_3$), 2.82 (3 H, s, CH_3-C2), 1.43 (t, J=7.0 Hz, CH_2CH_3). δ_C ($(CD_3)_2CO$) 175.37 (s, C-8), 164.92 (s, COO), 162.54 (s, C-2), 154.50 (s, C-8a), 138.46 (d, C-7), 136.42 (d, C-6), 129.98 (d, C-5), 129.59 (s, C-3a), 128.31 (d, C-4), 111.84 (s, C-3), 60.84 (t, *C*H_2CH$_3$), 14.72 (q, *C*H_3-C2), 14.05 (q, CH_2CH_3). *m*/*z* 232 (100, M^+), 204 (44, $[M-CO]^+$), 187 (36, $[M-OEt]^+$), 175 (96, $[M-CO-Et]^+$), 159 (40, $[M-CO_2Et]^+$), 131 (21, $[M-CO-CO_2Et]^+$), 77 (31), 43 (48). HR-MS: M^+, found 232.0735±0.001. $C_{13}H_{12}O_4^+$ requires 232.0736).

Reaction of [3,5,7-$^2H_3$]-2-tosyloxytropone (1b) with sodium ethyl acetoacetate

Following the same procedure—with the same amounts of reagents—as for the undeuterated compound, **2b** and **3b** were obtained as semi-solids in similar yields.

Data of [5,7-$^2H_2$]-3-acetyl-2*H*-cyclohepta[b]furan-2-one (2b). ν_{max} (Nujol) 1734, 1653 cm^{-1}. [Found: C 69.5; H 5.1. $C_{11}H_6D_2O_3$ requires C 69.47%, H 3.16%, D 2.10%]. δ_H ($CDCl_3$, 200 MHz) 9.20 (1 H, br.s, 4-H), 7.57 (1 H, br.s, 8-H), 7.42 (1 H, br.s, 6-H), 2.63 (3 H, s, CO*C*H_3). δ_C ($CDCl_3$, 50 MHz) 194.9 (s, *C*OCH_3), 167.6 (s, C-2), 134.9 (d, C-6), 131.7 (d, C-4), 120.1 (d, C-8), 30.1 (q, CO*C*H_3).

Data of [5,7-$^2H_2$]-2-methyl-3-ethoxycarbonyl-8*H*-cyclohepta[b]furan-8-one (3b). ν_{max} (Nujol) 1710 cm^{-1}. [Found: C 66.8; H 6.0. $C_{13}H_{10}D_2O_4$ requires C 66.67%, H 4.27%, D 1.71 %,]. δ_H ($CDCl_3$, 200 MHz) 8.35 (1 H, br.s, 4-H), 7.34 (1 H, br.s, 6-H), 4.42 (2 H, q, O*C*H_2CH$_3$), 2.82 (3 H, s, CH_3), 1.43 (3 H, t, OCH_2CH_3). δ_C ($CDCl_3$, 50 MHz) 175.4 (s, C-8), 165.0 (s, COO), 135.9 (d, C-6), 129.3 (d, C-4), 61.0 (t, *C*H_2CH$_3$), 15.2 (q, *C*H_3-C2), 14.4 (q, CH_2CH_3).

Reaction of 2-tosyloxytropone (1a) with sodium acetylacetonate

Using MeONa (0.116 g, 2.15 mmol), acetylacetone (0.26 mL, 2.53 mmol), and **1a** (0.260 g, 0.94 mmol) in DMSO (4 mL), we obtained **4a** (0.025 g, 0.12 mmol, 13%) as a colorless semi-solid, R_f 0.12, besides an orange colored, unidentified material (0.038 g), R_f 0.77.

Data of 2-methyl-3-acetyl-8*H*-cyclohepta[b]furan-8-one (4a). UV λ_{max}(MeOH) nm/(log ϵ) 350, 335, 320, 310 series of sh, 298 (3.70), 258 (3.96). ν_{max} (Nujol) 1666, 1611, 1577, 1515 cm^{-1}. δ_H ($(CD_3)_2CO$) 8.33 (1 H, ddd, J=0.8, 1.0, 11.3 Hz, 4-H), 7.15 (1 H, ddd, J=0.8, 8.6, 11.3 Hz, 5-H), 7.42 (1 H, ddd, J=1.0, 8.6, 12.4 Hz, 6-H), 7.16 (1 H, ddd, J=0.8, 0.8, 12.4 Hz, 7-H), 2.87 (3 H, s, $COCH_3$), 2.64 (s, CH_3-C2). δ_H ($CDCl_3$, 200 MHz) 8.40 (1 H, d, J=11.1 Hz,

4-H), 7.36 (1 H, m, 6-H), 7.29 (1 H, m, 7-H), 7.07 (1 H, ddd, J=1.1, 8.6, 1.0 Hz, 5-H), 2.87 (3 H, s, $COCH_3$), 2.63 (3 H, s, CH_3-C2). δ_C ($CDCl_3$, 50 MHz) 194.8 (s, *C*OCH_3), 173.4 (s, C-8), 163.9 (s, C-2), 138.4 (d, C-7), 136.4 (d, C-6), 129.9 (d, C-5), 128.9 (d, C-4), 31.5 (q, *COC*H_3), 15.7 (q, *C*H_3-C2). *m/z* 202 (76, M^+), 187 (11, $[M-Me]^+$), 174 (14, $[M-CO]^+$), 159 (100, $[M-MeCO]^+$), 131 (8, $[M-CO-COMe]^+$, 43 (33); HR-MS: M^+ found 202.0631±0.005. $C_{12}H_{10}O_3^+$ requires 202.0627.

Reaction of [3,5,7-$^2H_3$]-2-tosyloxytropone (1b) with sodium ethylacetoacetate

Following the same procedure—with the same amounts of reagents—as for the undeuterated analog, **4b** was obtained as a semi-solid in similar yield.

Data of [5,7-$^2H_2$]-2-methyl-3-acetyl-8H-cyclohepta[b]-furan-8-one (4b). ν_{max} (Nujol) 1667 cm^{-1}. [Found: C 71.1; H 5.7. $C_{12}H_8D_2O_3$ requires C 70.58%, H 3.92%, D 1.96%]. δ_H ($CDCl_3$, 200 MHz) 8.40 (1 H, br.s, 4-H), 7.36 (1 H, br.s, 6-H), 2.87 (3 H, s, $COCH_3$), 2.63 (3 H, s, CH_3).

Reaction of 2-tosyloxytropone (1a) with sodium diethyl malonate

Using MeONa (0.130 g, 2.4 mmol), diethyl malonate (0.44 mL, 2.9 mmol) and **1a** (0.298 g, 1.1 mmol) in DMSO (4 mL), we obtained **5** (0.098 g, 0.45 mmol, 42%), R_f 0.66 as a yellow crystalline solid, mp 129–130°C from Et_2O (lit.[3] 129–130°C).

Data of 3-ethoxycarbonyl-2*H*-cyclohepta[b]furan-2-one (5). UV λ_{max}(MeOH) nm/(log ϵ) 398 (3.9), 260, 247. ν_{max} (Nujol) 1764, 1689, 1654, 1587, 1531, 1270 cm^{-1}. δ_H ($(CD_3)_2CO$) 8.79 (1 H, ddd, J=0.8, 1.0, 11.4 Hz, 4-H), 7.82 (1 H, ddd, J=1.1, 8.9,11.4 Hz, 5-H), 7.71 (1 H, dddd, J=0.8, 1.0, 9.4, 10.5 Hz, 7-H), 7.63 (dd, J=1.4, 9.4 Hz, 8-H), 7.51 (1 H, dddd, J=0.8, 1.4, 8.9, 10.5 Hz, 6-H), 4.32 (2 H, q, CH_2CH_3), 1.34 (3 H, t, CH_2CH_3). δ_C ($(CD_3)_2CO$) 164.94 (s, COO), 163.87 (s, C-2), 159.32 (s, C-8a), 155.30 (s, C-3), 140.98 (d, C-5), 137.61 (d, C-7), 135.06 (d, C-6), 130.71 (d, C-4), 129.30 (s, C-3a), 120.06 (d, C-8), 60.57 (t, *C*H_2CH_3), 14.66 (q, CH_2CH_3). *m/z* 218 (60, M^+), 173 (100, $[M-OEt]^+$), 146 (97, $[M-CO_2Et]^+$), 89 (34), 63 (20). HR-MS: M^+ found 218.0571±0.005. $C_{12}H_{10}O_4^+$ requires 218.0576.

Reaction of 9-tosyloxyisocolchicide (15) with sodium diethyl malonate

Using MeONa (0.033 g, 0.61 mmol), diethyl malonate (0.130 mL, 0.86 mmol), and 9-tosyloxyisocolchicide (0.099 g, 0.18 mmol) in DMSO (2 mL), we obtained **16** (0.011 g, 0.023 mmol, 12%) as a yellow semi-solid, R_f 0.51. Eluting with $CHCl_3$/$(CH_3)_2CO$ 3:2, compound **15** was observed at R_f=0.45, accompanied by much colchiceine at R_f=0.14. UV analysis of the reaction mixture, based on molar absorption for isolated, pure **16**, showed that the latter was formed in 50% yield.

Data of (*S*)-*N*-(5,6,7,11-tetrahydro-1,2,3-trimethoxy-12-ethoxycarbonyl benzo[a]heptaleno[8,9-b]furan-11-one-7-yl) acetamide (16). UV λ_{max}(MeOH)/nm/(log ϵ) 431, 264, 220 (4.5) (in EtOH the absorption maxima are shifted to 433, 263, and 222 nm). CD λ ($\Delta\epsilon$) (EtOH) 270 (+11.3), 242 (+4.2), 215 (−9.9). ν_{max} (Nujol) 1756, 1751, 1650, 1582, 1516, 1467. δ_H ($(CD_3)_2CO$) 8.97 (1 H, s, 13-H), 7.98 (1 H, br. d, J=6.7 Hz, NH), 7.88 (1 H, d, J=10.4 Hz, 9a-H), 7.63 (1 H, d, J=10.4 Hz, 8-H), 6.82 (1 H, s, 4-H), 4.55 (1 H, ddd, J=4.1, 6.7, 12.8 Hz, 7-H), 4.27 (2 H, m, O*C*H_2CH_3), 3.93 (3 H, s, CH_3O-C3), 3.90 (3 H, 3 H, s, CH_3O-C2), 3.71 (s, CH_3O-C1), 2.66 (1 H, ddd, J=2.1, 5.0,12.8 Hz, 5-H *pro-S*), 2.34 (1 H, ddd, J=6.2, 12.8, 12.8 Hz, 5-H *pro-R*), 2.22 (1 H, ddd, J=6.2, 12.8, 12.8 Hz, 6-H *pro-S*), 1.99 (1 H, dddd, J=4.1, 5.0, 10.2,12.8 Hz, 6-H *pro-R*), 1.93 (3 H, s, $COCH_3$), 1.30 (3 H, t, J=7.0 Hz, OCH_2C*H*$_3$); NOE ($(CD_3)_2CO$): enhancements of 7% at 12-H on irradiation CH_3O-C1, and vice versa; 9% at 4-H on irradiation at CH_3O-C3; 4% at 4-H on irradiation at 5-H. δ_C ($(CD_3)_2CO$) 169.49 (s), 165.32 (s) 164.04 (s), 157.94 (s), 155.58 (s), 152.47 (s), 151.73 (s), 150.44 (s), 149.82 (s), 142.37 (s), 135.46 (s), 134.39 (d, C-13), 131.37 (d, C-9), 127.03 (s), 118.73 (d, C-8), 108.36 (d, C-4), 94.44 (s), 61.89 (q, *C*H_3O-C1), 61.18 (q, *C*H_3O-C2), 60.29 (t, O*C*H_2CH_3), 56.37 (q, *C*H_3O-C3), 53.39 (d, C-7), 37.62 (t, C-5), 22.60 (q, NHCO*C*H_3), 14.66 (q, OCH_2CH_3), while signals for C-6 were buried under the solvent signals. *m/z* 481 (2, $[M]^+$), 407 (4, $[M-NH_2COMe-Me]^+$), 368 (2), 28 (100); HR-MS: M^+ found 481.1722±0.005. $C_{26}H_{27}NO_8^+$ requires 481.1737).

Reaction of 10-tosyloxycolchicide (17) or 10-chloro-colchicide (18) with sodium diethyl malonate

MeONa (0.021 g, 0.39 mmol) and diethyl malonate (0.100 mL, 0.66 mmol) were mixed with **17** (0.062 g, 0.11 mmol) in DMSO (2 mL) and the mixture was stirred for 1 h. From the residue of work up, a TLC yellow spot at R_f 0.64 was extracted and subjected to reversed-phase HPLC, obtaining **19** (t_R 6.3 min, 0.001 g, 0.0021 mmol, 10%) and unreacted **17** (t_R 9.0 min, 0.049 g, 0.088 mmol, 80%). In a better procedure, **17** was replaced with 10-chloro-colchicide (**18**);[12] work up as above gave **19** (R_f 0.66, 0.025 g, 0.052 mmol, 29%) and unreacted **18** (R_f 0.49, 0.029 g, 0.072 mmol, 40%).

Data of (*S*)-*N*-(5,6,7,11a-tetrahydro-1,2,3-trimethoxy-11-ethoxycarbonyl benzo[a]heptaleno[7,8-b]furan-10-one-7-yl) acetamide (19). UV λ_{max}(MeOH) nm/(log ϵ) 425, 263, 235 (4.4). CD λ ($\Delta\epsilon$) (EtOH) 427 (−2.6), 330 (−3.6), 270 (+1.7), 235 (+7.6), 223 (−15.1). δ_H ($(CD_3)_2CO$) 8.66 (1 H, d, J=11.8 Hz, 12-H), 7.80 (1 H, d, J=11.8 Hz, 13-H), 7.78 (s, 8-H), 6.85 (1 H, s, 4-H), 4.56 (1 H, ddd, J=4.1, 6.7, 12.8 Hz, 7-H), 4.32 (2 H, m, O*C*H_2CH_3), 3.92 (3 H, s, CH_3O-C3), 3.88 (3 H, s, CH_3O-C2), 3.66 (3 H, s, CH_3O-C1), 2.66 (1 H, dddd, J=2.1, 5.0, 12.8 Hz, 5-H *pro-S*), 2.36 (1 H, ddd, J=6.2, 12.8, 12.8 Hz, 5-H *pro-R*), 2.22 (1 H, ddd, J=6.2, 12.8, 12.8 Hz, 6-H *pro-S*), 1.99 (1 H, dddd, J=4.1, 5.0, 12.8 Hz, 6-H *pro-R*),1.97 (3 H, s, $COCH_3$), 1.27 (3 H, t, J=7.0 Hz, OCH_2C*H*$_3$), NH not detected. *m/z* 481 (3, $[M]^+$), 407 (4, $[M-NH_2COMe-Me]^+$), 368 (1), 207 (2), 28 (100). HR-MS: M^+ found 481.1719±0.005. $C_{26}H_{27}NO_8^+$ requires 481.1737).

Acknowledgements

We thank A. Sterni for the MS spectra, and both MURST (Progetti di Interesse Nazionale) and CNR, Roma, for financial support.

References

1. Ridgby, J. A. *Tetrahedron* **1999**, *55*, 4521–4538.
2. Shimoma, F.; Kusaka, H.; Wada, K.; Azami, H.; Yasunami, M.; Suzuki, T.; Hagiwara, H.; Ando, M. *J. Org. Chem.* **1998**, *63*, 920–929.
3. Nozoe, T.; Takase, K.; Kato, M.; Nogi, T. *Tetrahedron* **1971**, *27*, 6023–6035.
4. Pietra, F. *Acc. Chem. Res.* **1979**, *12*, 132–138.
5. The least-strain conformer of **16** (Fig. 1) proved helpful in confirming the NMR assignments. Thus, the ^{1}H NMR coupling pattern in the segment C5–C7 matches the *J* values calculated by Altona's equation (Haasnoot, C. A. G.; De Leeuw, F. A. A. M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783–2792) for this conformer; in particular, (i) a H5*proS*–C5–C6–H6*proR* dihedral angle of 70° accounts for lack of a detectable coupling between these two protons and (ii) a H5*proR*–C5–C6–H6*proR* dihedral angle of 165° fits for the large coupling, J=12.8 Hz, between these two protons. Moreover, the conformer in the Fig. 1 accounts for the observed NOE enhancements between 4-H and both H5*proS* and MeO-C3 from one side, and between 13-H and MeO-C1 from the other side. For **16**, the least-strain conformer in the Fig. 1 was obtained by molecular mechanics calculations using the MM3(96) computer program from QCPE, Indiana University. In contrast, the computer program mmff94, as implemented into PC Spartan Pro, either V. 1.0 or 1.0.1 from Wavefunction, Inc., Irvine, CA, in our hands gave unreliable outputs. In a check with colchicine (Donaldson, W. A. *Tetrahedron* **1988**, *44*, 7409–7412; Berg, U.; Bladh, H. *Helv. Chim. Acta* **1999**, *82*, 323–325), mmff94 placed the NHAc group incorrectly into the pseudoaxial position. Also bulkier groups, in place of NHAc, could not be moved from the pseudoaxial to the pseudoequatorial position using mmff94 under the 'conformer distribution' option.
6. Cavazza, M.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2657–2661.
7. Cavazza, M.; Pietra, F. *Tetrahedron* **1998**, *54*, 14059–14064.
8. It is interesting that, in contrast, C-8 of colchicine is involved in Diels–Alder cycloadditions with strained alkynes (Brecht, R.; Haenel, F.; Seitz, G.; Frenzen, G.; Pilz, A.; Guénard, D. *Eur. J. Org. Chem.* **1998**, 2451–2460).
9. Brossi, A.; Yeh, H. J. C.; Chrzanowska, M.; Wolf, J.; Hamel, E.; Lin, C. M.; Quin, F.; Suffness, M.; Silverto *J. Med. Res. Rev.* **1988**, *8*, 77–94.
10. Berg, A.; Bladh, H. *Helv. Chim. Acta* **1999**, *82*, 323–325.
11. Nozoe, T.; Takase, K.; Nakazawa, T.; Fukuda, S. *Tetrahedron* **1971**, *27*, 3357–3368.
12. Cavazza, M.; Pietra, F. *Synth. Commun.* **1997**, *27*, 3405–3413.