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PAPER

Intramolecular reductive ketone–alkynoate coupling reaction promoted by (η^2-propene)titanium†

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Intramolecular reductive coupling of cycloalkanones tethered to alkynoates in the presence of (η^2-propene)titanium was successfully performed to provide hydroxy-esters in a diastereoselective manner. Subsequent lactonization afforded angularly fused unsaturated tricyclic lactones which represent relevant substructures of numerous bioactive compounds.

Introduction

Angularly fused 5-6-5 and 6-6-5 tricyclic fused lactones are relevant substructures for numerous bioactive compounds such as alliacolide,[1] alliacol A,[2] alliacol B[3] and arteannuin B[4] (Fig. 1).

The challenge associated with the synthesis of such tricyclic skeletons, combined with their pharmacological activities,[3] has elicited considerable synthetic interest. As part of our studies of the reactivity of acetylenic ω-ketoesters,[5] we planned an intramolecular ketone–alkynoate coupling reaction promoted by (η^2-propene)Ti(O*i*Pr)$_2$ (Sato's reagent) for the construction of polycyclic skeletons (Scheme 1).

The generation of divalent dialkyloxytitanium complexes and their utilization in organic synthesis have attracted considerable interest over a number of years.[6] Among these titanium complexes, the highly practical divalent (η^2-propene)Ti(O*i*Pr)$_2$ reagent, was introduced as an equivalent of Ti(O*i*Pr)$_2$.[7] Reactions of various acyclic alkynes with (η^2-propene)Ti(O*i*Pr)$_2$ have been intensively investigated,[6b,f,g,8] although the reaction with activated alkynes is less documented.[9] Indeed to the best of our knowledge, only one preliminary study has been published by Sato *et al.* involving a titanium-mediated cyclization, starting from 2-en-7-ynoates for the preparation of bicyclic systems.[10] Marek and coworkers reported an intramolecular cyclization, with a keto group at the γ- or δ-position affording four- and five-membered cycloalkanols.[11]

Thus reaction of an alkyne with a titanium(II) species should generate (η^2-alkynoate)Ti(O*i*Pr)$_2$ by ligand exchange of the coordinated propene in (η^2-propene)Ti(O*i*Pr)$_2$. That is, *in situ* reductive coupling reaction of the carbonyl group with the alkynoate complex could proceed to provide an oxytitanacycle. The hydrolysis of the latter would afford a bicyclic compound that includes an allylic alcohol at the bridgehead carbon. Thus, we prepared various cycloalkanones bearing an ynoate side chain.

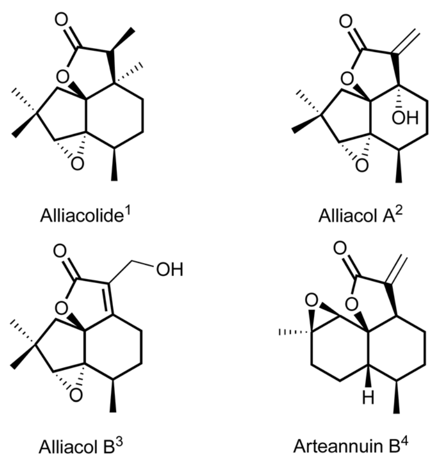
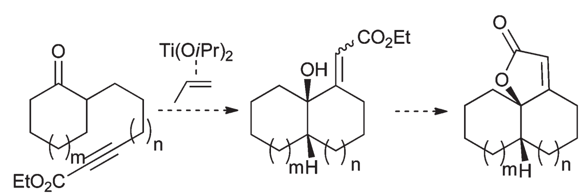


Fig. 1 Natural products containing tricyclic fused lactones.



Scheme 1

Results and discussion

Acetylenic ω-ketoesters **19–24** were synthesized starting from the corresponding *N*,*N*-dimethylhydrazones according to our previously developed reaction sequence (Scheme 2).[12]

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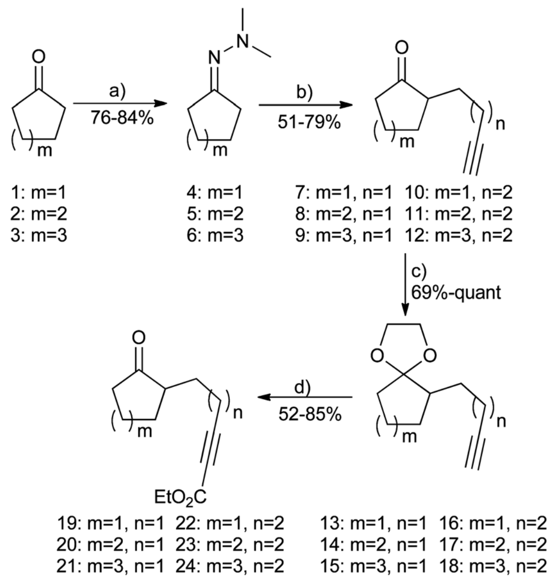
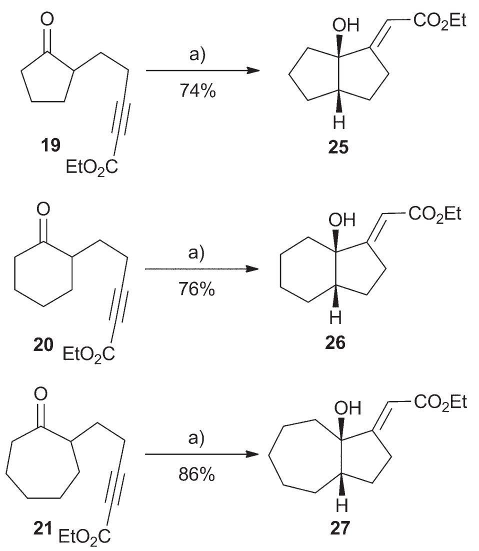
† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization of compounds and crystallographic data. CCDC 784204–784206. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob07049a



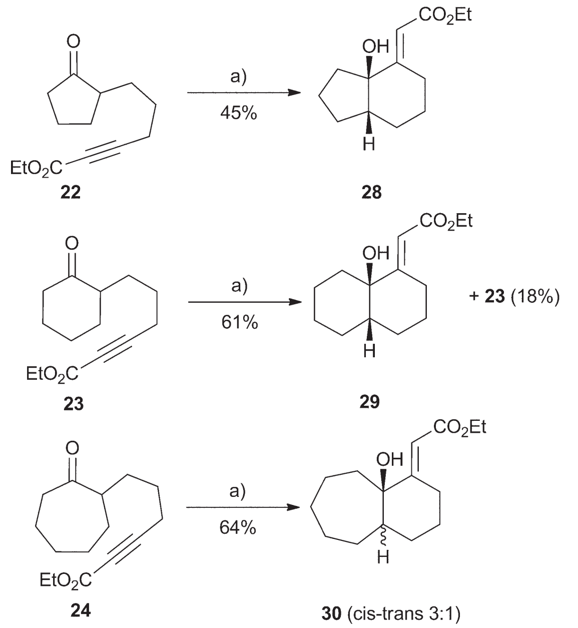
Scheme 2 Reagents and conditions: (a) H_2NNMe_2, TFA, benzene, reflux; (b) (1) *n*BuLi, (2) $I(CH_2)_{n+1}CCH$, (3) 10% HCl, THF, −40 °C to rt; (c) $HOCH_2CH_2OH$, PTSA, benzene, reflux; (d) (1) *n*BuLi, (2) ethyl chloroformate, (3) 10% HCl, −78 °C to rt.



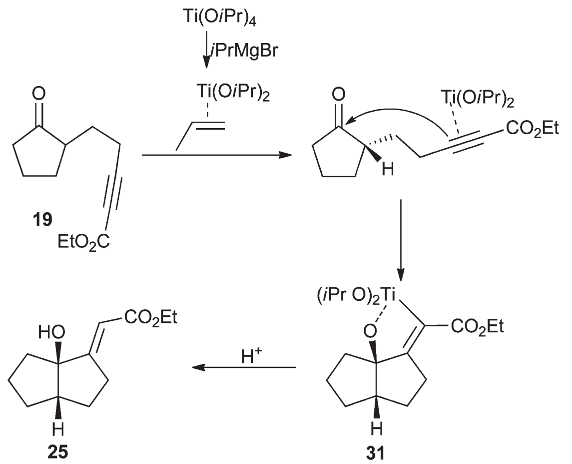
Scheme 3 Reagents and conditions: (a) 2 equiv. $Ti(OiPr)_4$, 6 equiv. *i*PrMgBr, Et_2O, −30 °C, 2 h.

To examine the feasibility of our synthetic strategy, we first investigated the carbometallation reaction of cycloalkanones bearing 7-ynoates. Compounds **19–21** (m = 1–3, n = 1) were treated with (η^2-propene)$Ti(OiPr)_2$, which was readily prepared by reacting $Ti(OiPr)_4$ with 2 equivalents of *i*PrMgBr. The reductive cyclization took place in a diastereoselective manner, providing exclusively cis-bicyclic ring systems bearing an *E*-substituted exocyclic electrophilic double bond (Scheme 3).

This reaction outlines an "umpolung" reaction of the ethoxycarbonyl substituted alkynes, since the titanocyclopropene generated *in situ* creates a nucleophilic center β to the ester.[13] Homologous 8-ynoates **22–24** underwent a similar *syn* selective



Scheme 4 Reagents and conditions: (a) 2 equiv. $Ti(OiPr)_4$, 6 equiv. *i*PrMgBr, Et_2O, −30 °C, 2 h.



Scheme 5 Proposed mechanism.

cyclization to give bicyclic alcohols **28–30** in a stereoselective fashion in moderate to good yields (Scheme 4).[14]

Mechanistic investigations

A possible reaction mechanism of cyclization is shown in Scheme 5. First, coordination of the alkyne moiety of **19** to the titanium(II) complex, followed by an intramolecular cyclization generates titanacycle **31** in a stereoselective fashion. Hydrolysis leads to the hydroxy *exo*-methylene ester compound **25**.

In order to probe the existence of a carbon–titanium bond as depicted in the oxatitanacycle **31**, iodine was added at the end of the reaction. The iodinolysis gave exclusively the *Z*-isomer of the corresponding alkenyl iodide **32** (Scheme 6).[11]

Asymmetric version

Because of the great importance of asymmetric synthesis and to broaden the scope of this cyclization, the optimal reaction conditions were extended to enantiomerically pure ynoates. Preparation of optically pure alkynoates **49** and **50** has already been described.[15]

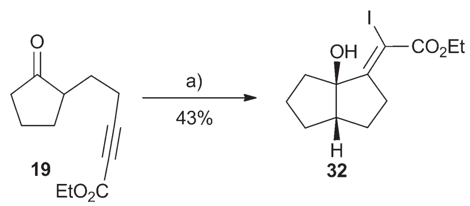
The synthesis of compounds **43** and **44** was carried out as follows: after protection of the carbonyl group, of enantioenriched ketoester derivatives **37** and **38**,[15] the ester functions were reduced to aldehydes **39** and **40**. A modified Corey–Fuchs reaction involving the addition of ethyl chloroformate prior to aqueous work-up afforded acetylenic ω-keto esters **43** and **44** with good yields (Scheme 7).

Treatment of **43–44** and **49–50** with Sato's reagent provided various bicyclic compounds having two consecutive stereogenic centres including a tetrasubstituted carbon in a stereoselective fashion. The carbometallation reaction worked well and isolated yields were good (Scheme 8). The structure of compounds **53** and **54** were unambiguously confirmed by X-ray crystallographic analysis (Fig. 2) though providing evidence for the exclusive formation of *E*-alkenes.

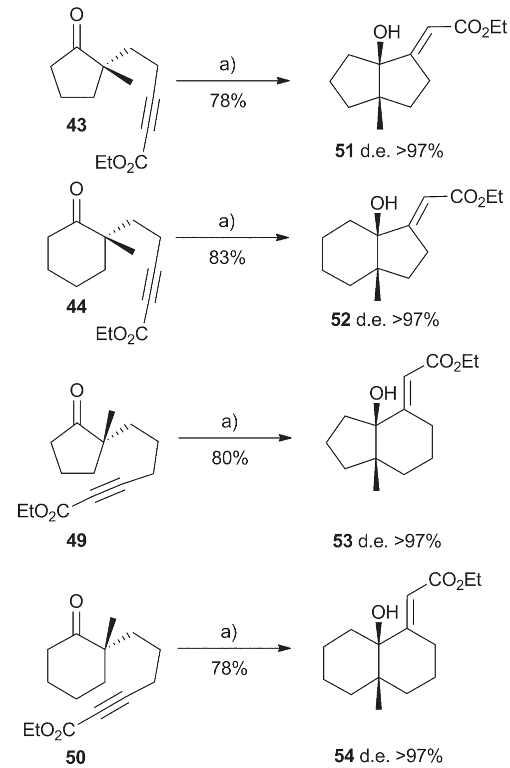
Lactonization reactions

The bifunctional molecules obtained provided an opportunity to approach tricyclic unsaturated lactones. The lactonization reaction using sodium ethanolate in refluxing ethanol starting from bicyclic compounds (**25–27** and **51–52**) issued from ω-ketoesters bearing a two carbon tether remained fruitless. In contrast, bicyclic compounds (**28–29** and **53–54**) derived from a three carbon tether afforded the corresponding unsaturated lactones in high yields (Scheme 9).

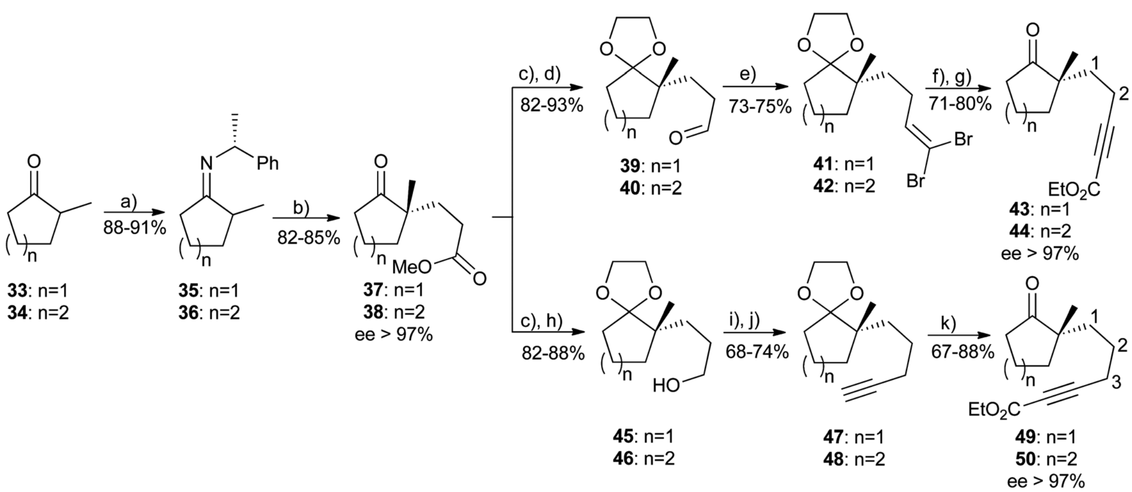
Lactonization reactions were also performed with enantiomerically pure compounds affording the corresponding lactones in



Scheme 6 Reagents and conditions: (a) (1) 2 equiv. $Ti(OiPr)_4$, 6 equiv. *i*PrMgBr, Et_2O, −30 °C, 2 h, (2) I_2, −78 °C to 0 °C, 25 min, (3) 1 N HCl.



Scheme 8 Reagents and conditions: (a) 2 equiv. $Ti(OiPr)_4$, 6 equiv. *i*PrMgBr, Et_2O, −30 °C, 2 h.



Scheme 7 Reagents and conditions: (a) (*R*)-α-methylbenzylamine, toluene, reflux; (b) methyl acrylate, PTSA, toluene, 40 °C; (c) ethylene glycol, nBu_4NBr_3, $HC(OEt)_3$, rt; (d) DIBAL-H, DCM, rt; (e) CBr_4, PPh_3, NEt_3, DCM, rt; (f) *n*BuLi, ethyl chloroformate, THF, −78 °C; (g) 10% HCl, THF, rt; (h) LAH, THF, rt; (i) TsCl, NEt_3, DMAP, DCM, rt; (j) lithium acetylide–ethylenediamine complex, DMSO, 0 °C to rt; (k) *n*BuLi, ethyl chloroformate, THF, −78 °C to rt then 10% HCl, rt.

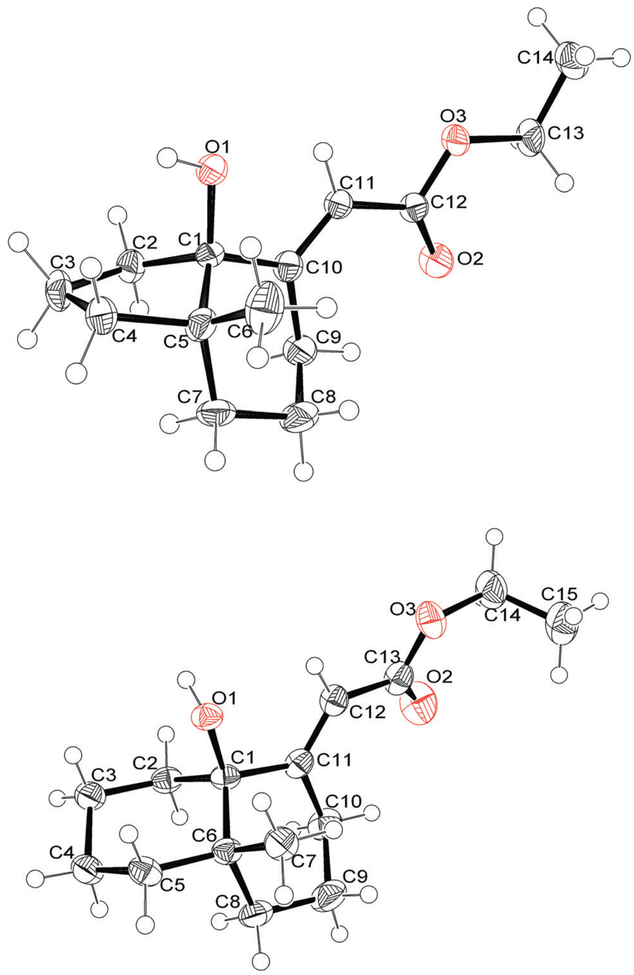
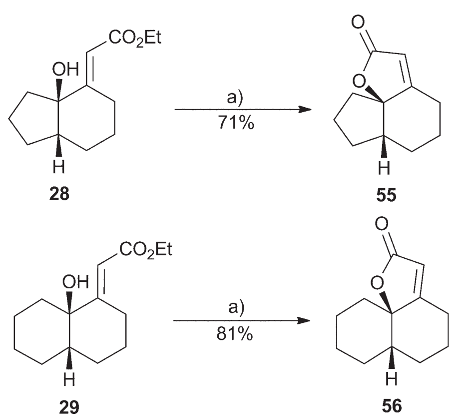


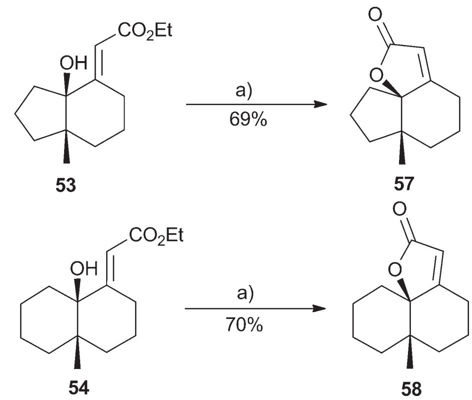
Fig. 2 ORTEP depiction of compounds **53** (top) and **54** (bottom) with thermal ellipsoids at the 50% probability level.[16]



Scheme 9 Lactonization reactions. Reagents and conditions: (a) 4 equiv. NaOEt, EtOH, reflux, 16 h.

good yields (Scheme 10). The structure of compound **58** was unambiguously confirmed by X-ray crystallographic analysis (Fig. 3).

Although the lactonization reaction was successful, the formation of the lactones stands in contrast with the stereochemistry



Scheme 10 Lactonization reactions: Asymmetric version. Reagents and conditions: (a) 4 equiv. NaOEt, EtOH, reflux, 16 h.

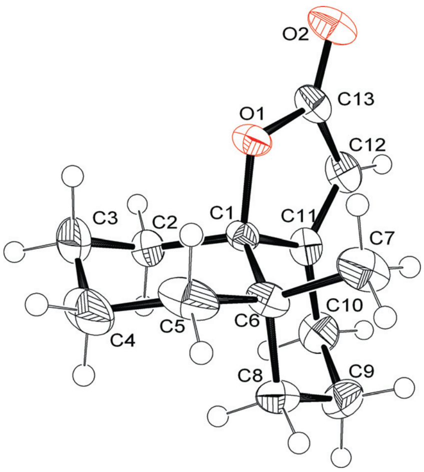


Fig. 3 ORTEP depiction of compound **58** with thermal ellipsoids at the 50% probability level.[17]

observed for the hydroxyl-esters. Based on this precedence, we hypothesized a double bond isomerization prior to lactonization *via* a Michael retro–Michael addition of ethanolate on the allylic ester or the reversible formation of an epoxide by intramolecular Michael reaction.

Conclusions

In conclusion, (η^2-propene)titanium promoted intramolecular reductive coupling reaction of cycloalkanones bearing activated alkynes provide bicyclic allylic alcohols in a stereoselective manner. This synthetically useful method was extended to various cycloalkanones bearing a 7-ynoate or 8-ynoate side chain. Although the lactonization reaction starting from m-5 bicyclic systems (compounds **25–27** and **51–52**) failed, unsaturated tricyclic lactones could be obtained starting from hydroxyesters **28–29** and **53–54**. Thus the tricyclic compounds obtained are present in numerous bioactive natural products. Further studies on synthetic applications of this methodology are under investigation.

Experimental section

Typical procedure for the preparation of bicyclic γ-hydroxy α,β-unsaturated esters

The starting material (0.6 mmol, 1 equiv.) was dissolved in 10 mL of dry Et_2O and cooled to −30 °C. $Ti(OiPr)_4$ (1.2 mmol, 2 equiv.) was added under vigorous stirring. Then *i*PrMgBr (3.6 mmol, 6 equiv.) was added dropwise. The reaction mixture was stirred at −30 °C for 2 h, then hydrolysed with 10 mL of 10% HCl at −30 °C, warmed to rt and stirred for 30 min. The aqueous phase was extracted with 2 × 25 mL of Et_2O and 2 × 25 mL of EtOAc. The combined organic layers were consecutively washed with 25 mL of a saturated aqueous solution of $NaHCO_3$, 15 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar). The pure product was obtained by column chromatography (petroleum ether–EtOAc 95 : 5).

(*E*)-Ethyl-2-((4a*S*,8a*R*)-8a-hydroxy-4a-methyloctahydronaphthalen-1(2H)-ylidene)acetate 54. Yield: 78%; colourless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 3H), 1.07–1.25 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H), 1.45–1.77 (m, 9H), 1.93–2.21 (m, 3H), 3.90 (d, J = 14.3 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 6.11 (d, J = 1.8 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 21.0, 21.5, 22.3, 22.7, 26.6, 33.6, 34.0, 35.9, 39.7, 59.8, 77.4, 112.4, 166.3, 167.5 ppm; IR (neat) 3516, 2926, 2864, 1696, 1638 cm^{-1}; HRMS Cal for $[M + Na]^+$: $C_{15}H_{24}O_3$: 275.1618 Found: 275.1611; $[\alpha]_D^{20}$ = +39.24 (c = 0.576, $CHCl_3$).

Typical procedure for the preparation of tricyclic α,β-unsaturated lactons

A solution of sodium (4 equiv.) in dry EtOH (10 mL) was added to a solution of the bicyclic γ-hydroxy α,β-unsaturated esters (0.5 mmol, 1 equiv.) in 6 mL of dry EtOH. The resulting mixture was refluxed for 16 h. After cooling to rt the solvent was removed. The resulting slime was dissolved in 15 mL of Et_2O and treated with 8 mL of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with 3 × 15 mL of Et_2O. The combined organic layers were washed with 20 mL of a saturated aqueous solution of NaCl, dried over anhydrous Na_2SO_4 and concentrated in vacuum (15 mbar). The pure product was obtained by column chromatography (petroleum ether–EtOAc 95 : 5).

(6a*S*,10a*R*)-6a-Methyl-4,5,6,6a,7,8,9,10-octahydro-2H-naphtho-[8a,1-b]furan-2-one 58. Yield: 70%; colourless solid; ^{1}H NMR (300 MHz, C_6D_6) δ 0.61 (s, 3H), 0.84–1.27 (m, 6H), 1.28–1.43 (m, 4H), 1.43–1.69 (m, 3H), 1.93 (ddt, J = 13.9, 4.6, 1.8Hz, 1H), 5.35 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (75 MHz, C_6D_6) δ 20.8, 21.2, 22.2, 22.6, 25.9, 30.2, 32.3, 36.5, 39.6, 88.6, 113.4, 172.0, 172.7 ppm; IR (neat) 2927, 2864, 1731, 1235 cm^{-1}; HRMS Cal for $[M + Na]^+$: $C_{13}H_{18}O_2$: 229.1199 Found: 229.1205; $[\alpha]_D^{20}$ = −40.17 (c = 0.605, $CHCl_3$).

Acknowledgements

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17 CCDC-784205 contains the supplementary crystallographic data for compound **58**.