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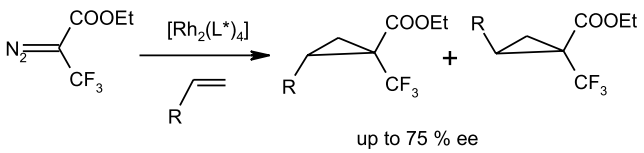
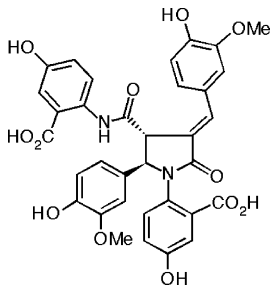
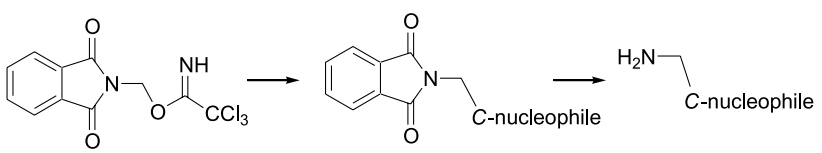
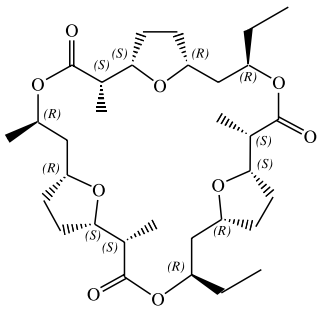
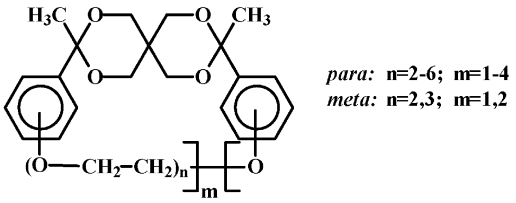


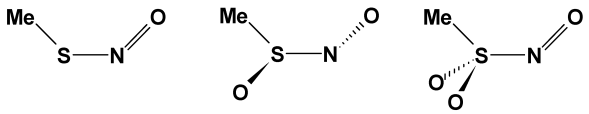


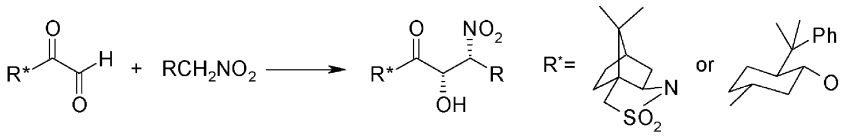
A novel cyclic dehydrodimer of avenanthramide phytoalexin, named bisavenanthramide B was isolated from elicited oats. Its structure was determined based on spectroscopic data and chemical derivatization.

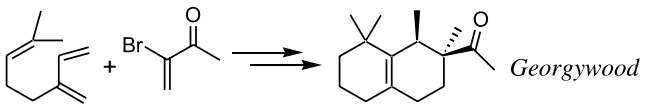


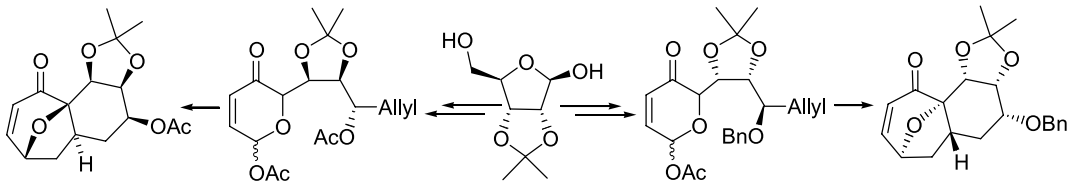


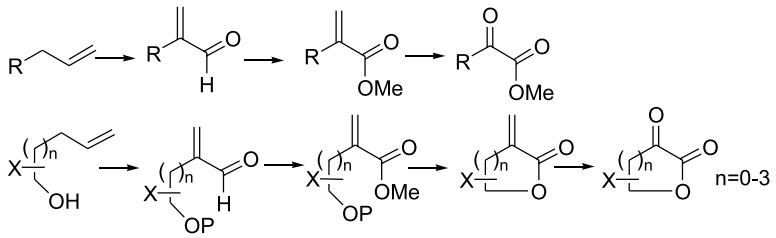


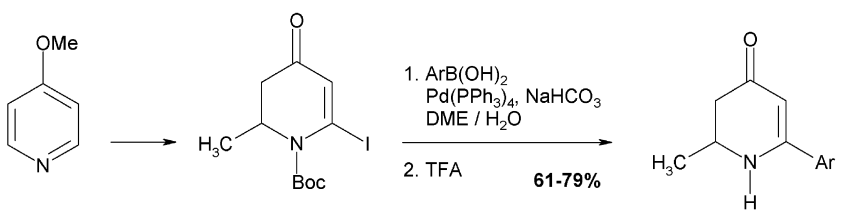


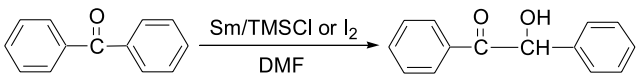


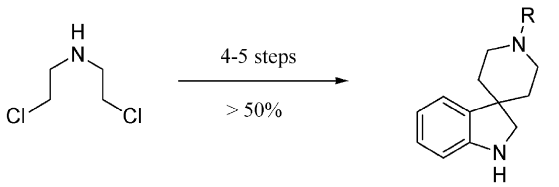












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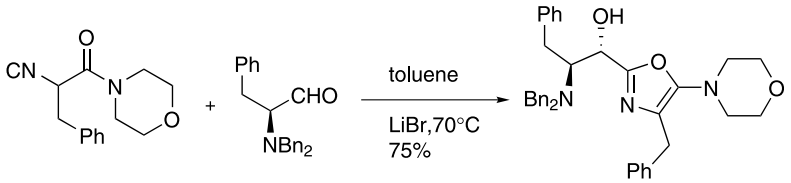

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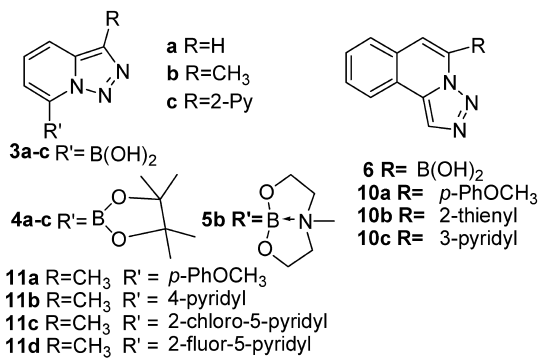
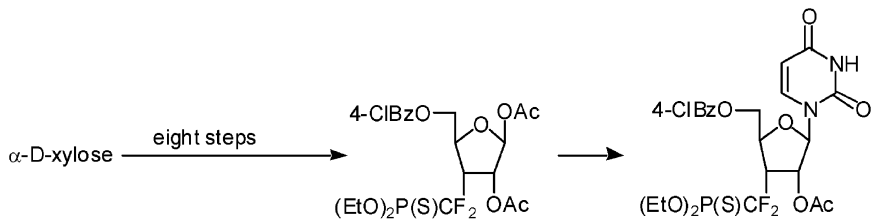
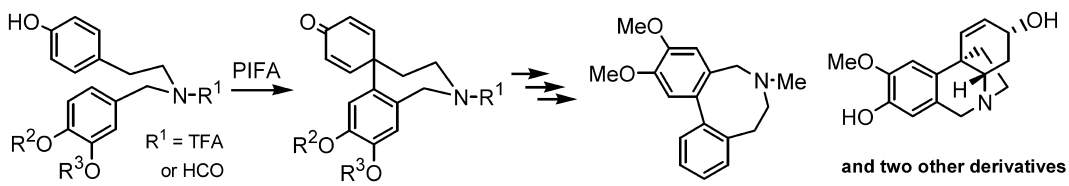
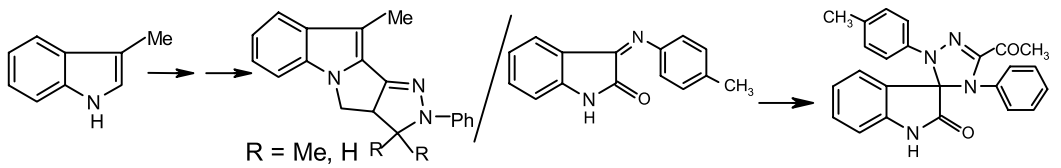
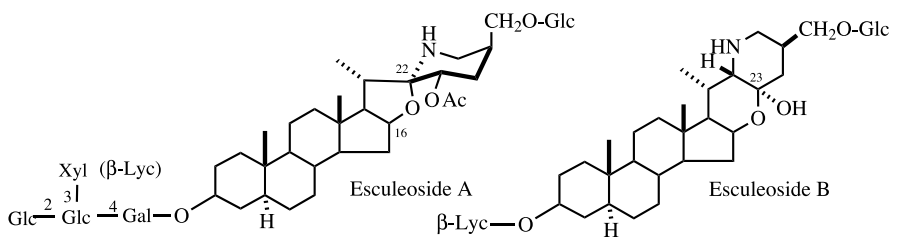


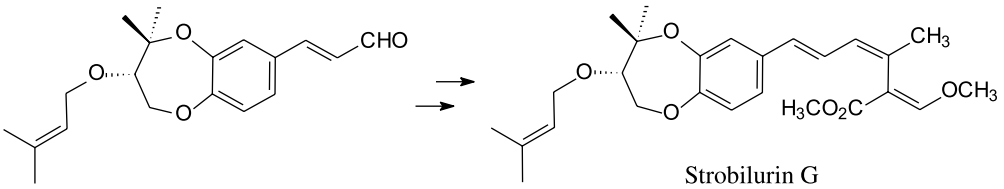
Novel triazolopyridylboronic derivatives **3a**–**c**, **4a**–**c**, **5** and **6** are synthesized and used to obtain compounds **11a**–**d**, and **10a**–**c** in Suzuki-type reactions.



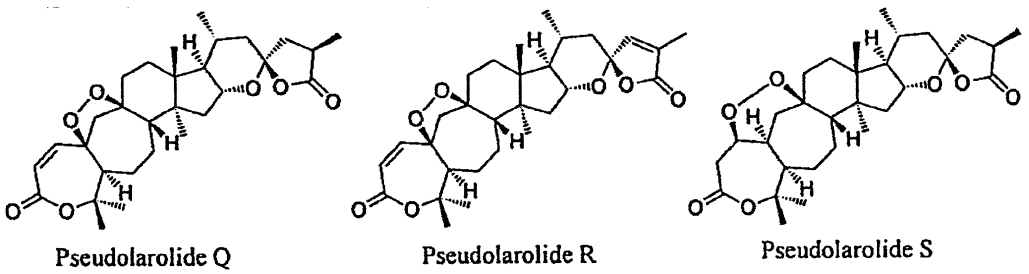








Strobilurin G



Pseudolarolide Q Pseudolarolide R Pseudolarolide S

Pseudolarolides Q, R, S, have been isolated from the leaves of *Pseudolarix kaempferi*.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Rh(II)-Catalyzed asymmetric carbene transfer with ethyl 3,3,3-trifluoro-2-diazopropionate

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Abstract—The asymmetric cyclopropanation of 1,1-diphenylethylene (**2**) with ethyl 3,3,3-trifluoro-2-diazopropionate (**1**) in the presence of chiral Rh(II) catalysts affords cyclopropane **3** with yields and enantioselectivities of up to 72 and 40%, respectively. Similar results are obtained for asymmetric cyclopropenation of hex-1-yne (**4**), although enantioselectivity is lower. The cyclopropanation of mono-substituted olefins (**8a**–**8e**) with **1** leads to *cis*/*trans*-mixtures of cyclopropanes **9a**–**9e** with a maximum ee of 75% for 4-methoxystyrene (**8c**).

1. Introduction

Fluoro substituents exert a profound influence on the biological properties of organic compounds, and are, therefore, of great interest in the pharmaceutical and agrochemical industry.[1] Among the current methodologies for the introduction of trifluoromethyl groups[2] the ones involving the trifluoromethyl anion, which is available from (trifluoromethyl)trimethylsilane[3] or trifluoroacetaldehyde hemiaminals,[4] occupy a prominent position. A variant of this approach involves photoinduced reduction of trifluoromethyl iodide by tetrakis-(dimethylamino)ethylene.[5] Alternatively the trifluoromethyl (or more precisely, trifluoro-ethyl) group may be introduced via trifluoromethyl-substituted carbenes. The transition metal-catalyzed decomposition of alkyl 3,3,3-trifluoro-2-diazopropionate leads to typical carbenoid reactions with appropriate substrates, such as cyclopropanations of electron-rich double bonds,[6] cycloadditions to nitriles,[7] insertions into OH bonds,[8] and formation of ylides with amines,[9] sulfides[10] and aromatic aldehydes.[11] The trifluoro-2-diazopropanoyl moiety has also been used for photoaffinity labeling of proteins via insertion into NH bonds.[12]

3,3,3-Trifluoro-2-diazopropionates are prepared from trifluoromethyl pyruvate esters via the tosylhydrazones. In the past, the fluorinated pyruvates had to be synthesized from bromotrifluoromethane and oxalic ester using a modified Barbier procedure.[6,13] Nowadays, trifluoromethyl pyruvates are commercially available and the preparation of the diazo precursor of the trifluoromethyl substituted carbene is easy.

To the best of our knowledge, no asymmetric reactions with trifluoromethyl substituted carbenes have yet been reported in the literature. We have now extended our methodology for asymmetric carbene transfer based on diazo decomposition with chiral non-racemic Rh(II)-catalysts[14] to ethyl 3,3,3-trifluoro-2-diazopropionate (**1**), and report our first results for olefin cyclopropanation.

2. Results and discussion

2.1. Carbenoid reactions of ethyl 3,3,3-trifluoro-2-diazopropionate (1) in the presence of [$Rh_2(OAc)_4$]

A representative selection of substrates was selected in order to evaluate the potential of diazo decomposition of **1** with [$Rh_2(OAc)_4$]. The reactions were carried out by syringe pump addition of **1** in CH_2Cl_2 to the appropriate substrate in CH_2Cl_2 at room temperature in the presence of 5% (with respect to **1**) of [$Rh_2(OAc)_4$] (see Section 4).

The structure of the products was established by means of their spectral data. They are straightforward and deserve no particular comment. The presence of the trifluoromethyl group is evidenced by a quadruplet in the ^{13}C NMR at ca. 125 ppm, while the carbon adjacent to the CF_3 group appeared as quadruplet at 39.2 in **3**, 31.2 in **5**, and in the range of 31–35 ppm in the cyclopropanes **9a**–**9e** (Scheme 1).

A selection of chiral, non-racemic Rh(II) carboxylate-catalysts (see Chart 1) which were available in our laboratory were examined for enantioselective cyclopropanation of **2**, and the results are summarized in Table 1. Yields of cyclopropane **3** were in the range of

Keywords: Metal carbene; Cyclopropanation; Rh(II)-catalysts; Asymmetric carbene transfer.
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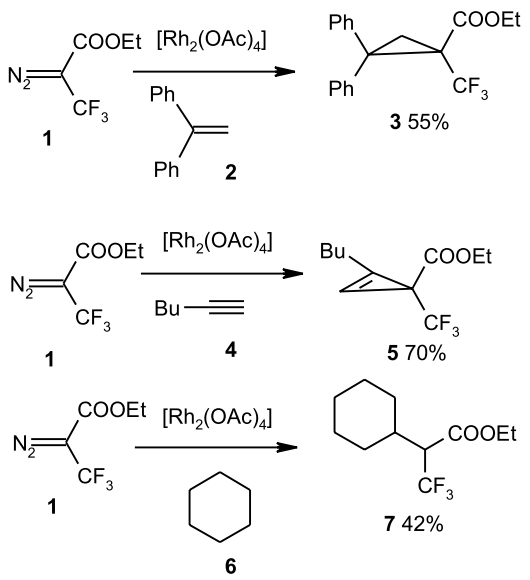


Scheme 1.

36–72%, and enantioselectivities varied from 0 to 42%. The $[Rh_2\{(S)\text{-dosp}\}_4]$ catalyst of Davies[15] was superior than the other catalysts with respect to enantioselectivity, but $[Rh_2\{(S)\text{-nttl}\}_4]$ and $[Rh_2\{(S)\text{-pttl}\}_4]$ were of comparable selectivity. An analogous series of experiments was realized for cyclopropenation of hex-1-yne (**4**) which afforded the cycloprop-2-ene-1-carboxylate **5** in 34–76% yield. Enantioselectivities were significantly lower, however,

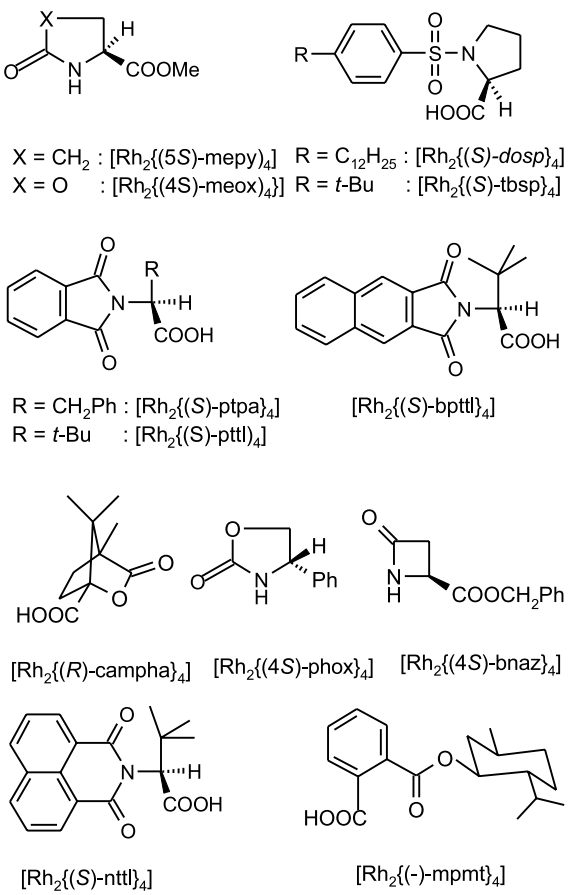


Chart 1.

Table 1. Cyclopropanation of 1,1-diphenylethylene (**2**) and cyclopropenation of hex-1-yne (**4**) with ethyl 3,3,3-trifluoro-2-diazopropionate (**1**)[a]

Catalyst	Yield **3** (%)	ee[b] (%)	Yield **5** (%)	ee[c] (%)
$[Rh_2(OAc)_4]$	54	—	55	—
$[Rh_2\{(S)\text{-ptpa}\}_4]$	65	26	60	01
$[Rh_2\{(S)\text{-tbsp}\}_4]$	36	20	51	16
$[Rh_2\{(S)\text{-dosp}\}_4]$	53	42	76	14
$[Rh_2\{(S)\text{-nttl}\}_4]$	72	40	51	24
$[Rh_2\{(S)\text{-pttl}\}_4]$	44	40	17	15
$[Rh_2\{(S)\text{-bpttl}\}_4]$	53	26	70	14
$[Rh_2\{(S)\text{ campha}\}_4]$	66	0	34	02
$[Rh_2\{(5S)\text{-msi}\}_4]$	48	01	—	—
$[Rh_2\{(3S)\text{-bnaz}\}_4]$[c]	36	04	—	—

[a] In CH_2Cl_2, room temperature, 5% of catalyst.
[b] By HPLC with OD-H column, hexane/isopropanol 99:1.
[c] By GC, β-Dex column, 120 °C.

and culminated at 24% ee with $[Rh_2\{(S)\text{-nttl}\}_4]$. The absolute configuration of the products was not determined owing to their low enantiopurity. No enantio-selective CH insertions were attempted at this time.

2.2. Cyclopropanation of styrene (8a) with ethyl 1,1,1-trifluoro-2-diazopropionate (1)

The reaction of styrene (**8a**) with **1** afforded a ca. 1:1 mixture of *cis*-and *trans*-stereoisomers of **9a** in 75–90% yield. Isomer separation was achieved by column chromatography on silica gel. Base-catalyzed hydrolysis of the mixture of stereoisomers of **9a** proceeded stereoselectively to *cis*-**10** while *trans*-**9a** was recovered unchanged. Since *trans*-2-substituted cyclo-propanecarboxylic esters are known to be hydrolyzed at higher rates their more hindered *cis*-substituted isomers,[16] the *cis*-configuration was tentatively assigned to the hydrolysis product of **9a**. Note that according to the CIP rules the triflurometyl has higher priority than the carboxy group, so that the *cis* isomers of this series of cyclopropanes have the phenyl and carboxylate groups in a *trans* orientation (Fig. 1).[17] The acid *cis*-**10** was transformed to the *cis*-*p*-bromophenacyl ester **11** wich afforded crystals suitable for X-ray analysis. The X-ray structure of **11** confirms the tentatively assigned *cis* configuration of **9a** (Fig. 2). Base-induced hydrolysis of unreacted *trans*-**9a**, in turn, afforded *trans*-**10**.

Reduction of *trans*-**9a** with $LiAlH_4$ afforded the *trans* alcohol **12** while *cis*-**12** was obtained upon reduction of the mixture of stereoisomers of **9a** followed by chromatographic separation. Attempts to obtain crystals suitable for X-ray analysis form salts of the acid *cis*-**10** or from the OPNB derivative of *cis*-**12** were not successful (Scheme 2).

The results for cyclopropanation of styrene (**8a**)with chiral non-racemic Rh(II)-catalysts are presented in Table 2. The carboxylate ligands afforded generally satisfactory yields at

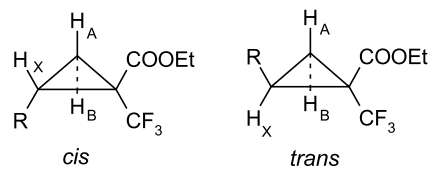


Figure 1.

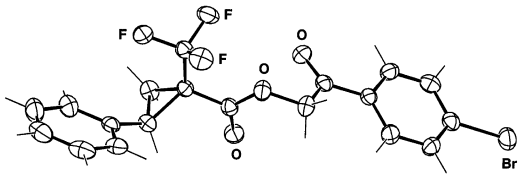
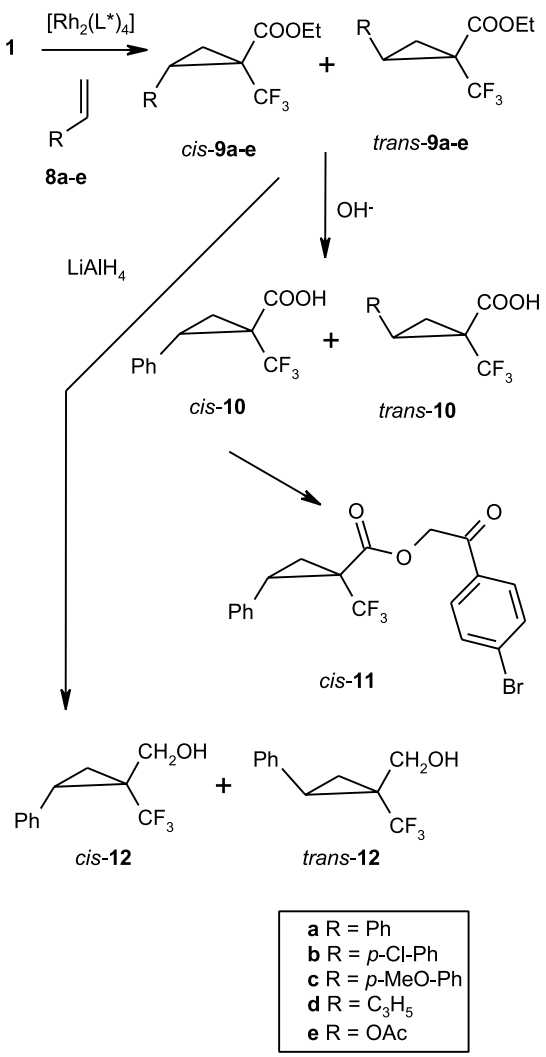


Figure 2. Perspective view of the crystal structure of *cis*-**11**. Ellipsoids are represented with 40% probability.

25 °C, but were less efficient than $[Rh_2(OAc)_4]$. Rh(II)-carboxamidate catalysts, in turn, were less reactive and required heating to 80 °C (in dichloroethane, DCE). Yields and enantio-selectivities were generally lower with Rh(II)-carboxamidates than with Rh(II)-carboxylates. The *cis*/*trans* ratios were found close to 50:50±10%, with $[Rh_2\{(4S)\text{-meox}\}_4]$ at the extreme with 30:70, and the enantioselectivity was in all cases higher for the *trans*-isomer. Among the carboxylate catalysts $[Rh_2\{(S)\text{-dosp}\}_4]$ afforded the highest ee of 50% for *trans*-**9a**, and 18% for *cis*-**9a**. Doyle's $[Rh_2\{(3S)\text{-bnaz}\}_4]$ catalyst[18] was found as selective as the dosp-catalyst of Davies for formation of *trans*-**9a**, although less so for formation of *cis*-**9a**.



Scheme 2.

Table 2. Cyclopropanation of styrene (**8a**) with ethyl 3,3,3-trifluoro-2-diazopropionate (**1**)[a]

Catalyst	Yield **9a** (%)	*cis*/*trans*	*cis*-**9a** ee[b] (%)	*trans*-**9a** ee[b] (%)
$[Rh_2(OAc)_4]$	90	50:50	—	—
$[Rh_2\{(S)\text{-ptpa}\}_4]$	64	43:57	16	24
$[Rh_2\{(S)\text{-tbsp}\}_4]$	44	60:40	18	24
$[Rh_2\{(S)\text{-dosp}\}_4]$	58	44:56	18	50
$[Rh_2\{(S)\text{-nttl}\}_4]$	50	45:55	14	22
$[Rh_2\{(S)\text{-campha}\}_4]$	72	52:48	08	32
$[Rh_2\{(S)\text{-mpmt}\}_4]$	50	40:60	02	00
$[Rh_2\{(5S)\text{-mepy}\}_4]$[c]	43	40:60	04	00
$[Rh_2\{(4S)\text{-meox}\}_4]$[c]	24	30:70	00	00
$[Rh_2\{(3S)\text{-bnaz}\}_4]$[c]	36	46:54	04	50
$[Rh_2\{(4R)\text{-phox}\}_4]$[c]	36	43:57	08	42

[a] With 5% of $[Rh_2(OAc)_4]$ in CH_2Cl_2 at room temperature.
[b] Determined by GC (β-Dex, 120 °C).
[c] In DCE, 80 °C.

2.3. Cyclopropanation of other olefins (8b–e)

A few other terminal monosubstituted olefins were subjected to the enantioselective cyclopropanation procedure with $[Rh_2\{(S)\text{-dosp}\}_4]$. The isomers of the cyclopropane **9b**, derived from *p*-chlorostyrene (**8b**) were fully separated, and *trans*-**9d** was separated from the mixture resulting from reaction of pentene. In the other cases preparative separation of the stereoisomers failed and the spectra were assigned with the mixtures of stereoisomers.

The relative configurations of the phenyl-substituted cyclopropanes were determined upon comparison of the NMR data with those of **9a**, for which it is unambiguously established (see above). The protons of the cyclopropane rings constitute an ABX system (see Fig. 1). The signals of the *trans*-esters **9a–9c** as well as those of the *trans*-acid **10** are well separated. Contrary to expectation,[21] the coupling constants J_{AX} and J_{BX} were found practically identical, and could not be used for assignment of the relative configuration of the cyclopropanes. In the *trans* isomers of these cyclopropanes the signal of H_X (corresponding to H–C(2)) appeared as a triplet separated by ca. 0.7 ppm downfield from the other cyclopropane protons. H_A was identified because of its weak coupling with the CF_3 group *trans* at C(1), which lead either to a fine structure of the triplet, or at least to line broadening (W-coupling).[22] In contrast, H_B appeared as a neat part of an ABX system devoid of F-coupling. In the corresponding *cis*-cyclopropanes H_A and H_B resonated in a very small range, or even coincided (Table 3). In addition, H–C(2), C(2), and the carbonyl carbon appeared always at lower field in the *cis*-isomers, and their ^{19}F resonances were found at ca. 5 ppm lower field. The protons of the OCH_2 group of the *trans*-esters **9a–9c** were shifted upfield by ca. 0.4 ppm, owing to the presence of the *cis*-phenyl group, and an analogous, although somewhat weaker shift of 0.3–0.4 ppm occurred in the methyl groups of the esters. These shifts are in agreement with those observed for ethyl *cis*-2-phenylcyclopropane carboxylate which is upfield by 0.3 ppm in comparison to that of the *trans* esters.[23] The assignments are further supported by NOE's H_A/Ph for *trans*-**9a**, H_B/Ph for *cis*-**9a**, and H_A/Ph for *trans*-**9b**, and are consistent with those reported in the literature for the amides **13**. The ABX

Table 3. Selected NMR data of *cis*- and *trans*-cyclopropanes

Cpd	R	X	δH–C(2)	δH_A	δH_B	δH (OCH_2)	δC(2)	δC(C=O)	$\delta\,^{19}F$[a]
cis-**9a**	Ph	COOEt	3.06–3.09	1.91–1.97	1.91–1.97	4.23–4.29	32.2	168.3	−61
trans-**9a**	Ph	COOEt	2.91–2.95	2.13–2.15	1.77–1.80	3.78–3.89	29.0	165.0	−67
cis-**9b**	4-Cl-Ph	COOEt	3.02–3.05	1.93–1.98	1.87–1.90	4.26–4.35	31.8	168.0	−61
trans-**9b**	4-Cl-Ph	COOEt	2.89–2.92	2.13–2.16	1.76–1.82	3.92–3.96	28.5	164.9	−67
cis-**9c**	4-MeO-Ph	COOEt	3.01–3.05	1.91–1.96	1.88–1.91	4.26–4.35	31.7	168.0	−61
trans-**9c**	4-MeO-Ph	COOEt	2.88–2.91	2.10–2.15	1.73–1.78	3.89–3.94	28.6	165.2	−67
cis-**9d**	C_3H_5	COOEt	1.60–1.75	1.57–1.71	1.57–1.71	4.25–4.35	29.0	168.9	−61
trans-**9d**	C_3H_5	COOEt	1.59–1.66	1.34–1.55	1.34–1.55	4.15–4.25	25.7	166.9	−67
cis-**9e**	OAc	COOEt	4.58–4.64	1.89–1.94	1.85–1.89	4.21–4.28	56.5	166.3	−62
trans-**9a**	OAc	COOEt	4.46–4.50	2.06–2.08	1.71–1.75	4.20–4.32	54.0	163.8	−66
cis-**10**	Ph	COOH	3.23–3.26	2.05–2.07	2.05–2.07	—	32.8	174.4	−62
trans-**10**	Ph	COOH	3.02–3.04	2.12–2.14	1.82–1.85	—	30.3	169.1	−67
cis-**11**	Ph	*p*-BrX[b]	3.27–3.30	2.07–2.13	2.03–2.07	—	32.9	166.0	−61
cis-**12**	Ph	CH_2OH	2.58–2.59	1.25–1.33	1.63–1.67	3.75–4.01[c]	26.7	—	−63
trans-**12**	Ph	CH_2OH	2.74–2.78	1.46–1.51	1.37–1.41	3.46–3.65[c]	24.9	—	−69
cis-**13**	Ph	$CONH_2$	3.10[d]	1.98	1.83	—	—		−59.7[e]
trans-**13**	Ph	$CONH_2$	2.75[d]	2.10	1.57				−65.7[f]

[a] Relative to $CFCl_3$.
[b] X=*p*-bromophenacyl.
[c] For protons of the CH_2OH group.
[d] Ref. 19.
[e] From 19.23 ppm downfield relative to CF_3COOH, Ref. 19 with $\delta(CFCl_3)=\delta(CF_3COOH)$ −77 ppm.[20]
[f] From 12.56 ppm downfield relative to CF_3COOH, Ref. 19.

system of the alcohols **12** obtained by LAH reduction of the esters **9a** is shifted upfield by ca. 0.3–0.7 ppm in comparison to that of the ester precursors. Now the signals of *cis*-**12** are better separated than those of *trans*-**12**. The CH_2OH protons of the *trans*-isomer of **12** (where the phenyl and COOEt groups are *cis*) are again shifted upfield by ca. 0.3 ppm in comparison to those of *cis*-**12**, and behave in analogy to those of 2-phenylcyclopropylmethanol, where they are shifted upfield by 0.3 ppm when the phenyl group is *cis*.[24] The *cis*-isomer of **12** exhibited NOE's between H–C(2)/CH_2OH, H_A/CH_2OH and H_B/Ph in support of the stereochemical assignment based on chemical correlations. With *trans*-**12** an NOE was observed for H_A/Ph. The stereochemical assignment of the *cis*-cyclopropane **9e** derived from reaction with vinyl acetate is based on H, F coupling between the trifluoromethyl group with the *trans*-protons H_A and H–C(2), while those of the isomers of **9d** (from reaction with pentene (**8d**)) are based on the ^{13}C resonances of the ester carbonyl and ^{19}F chemical shifts of the CF_3 substituent, in analogy to the assignments of the esters **9a**–**9c**. Unfortunately, NOE experiments to confirm the assignments were ambiguous, and in these cases the stereochemistry may be inverted.

The results for cyclopropanation of these olefins with **1** in the presence of $[Rh_2\{(S)\text{-dosp}\}_4]$ are summarized in Table 4. The reactions afforded *cis*/*trans* mixtures of cyclopropanes in yields ranging from 33–80%, and enantioselectivities from 12–22 for the *cis*- and 16–75% for the *trans*-isomers. In contrast, no cyclopropanation occurred with *trans*-oct-4-ene, *trans*-β-methylstyrene and *trans*-stilbene.

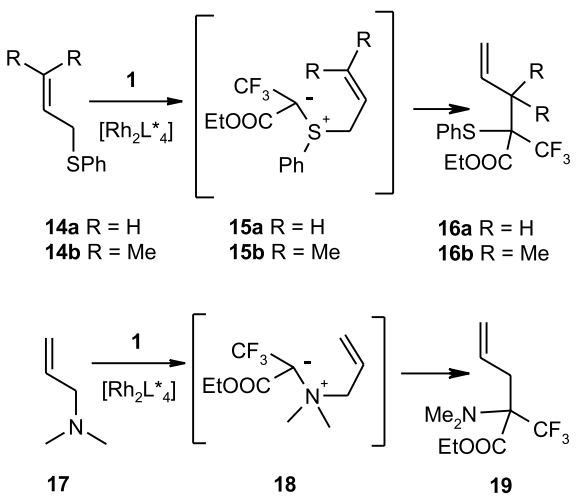
Table 4. Cyclopropanation of olefins **8b**–**8e** with ethyl 3,3,3-trifluoro-2-diazopropionate (**1**) in the presence of $[Rh_2\{(S)\text{-dosp}\}_4]$[a]

Cpd	R	Yield (%)	*cis*/*trans*	ee *cis*(%)[b]	ee *trans* (%)[b]
9b	4-Cl-Ph	52	51:49	12	43
9c	4-MeO-Ph	80	23:77	12	75
9d	C_3H_5	68	42:58	16	12
9e	OAc	33	69:31	22	44
9e	OAc[c]	10	54:46	4	57

[a] In CH_2Cl_2, room temperature.
[b] By GC, with β-Dex column.
[c] With $[Rh_2\{(S)\text{-tbsp}\}_4]$.

2.4. Formation and rearrangement of ammonium and sulfonium ylides

The carbene derived from ethyl 1,1,1-trifluoro-2-diazopropionate (**1**) is known to form ylides with heteroatoms having lone pairs, and the ylides form stable products upon [2,3]-sigmatropic or Stevens rearrangements. We have investigated the enantioselectivity of the diazo decomposition of **1** in the presence of allylphenyl sulfide (**14a**) and its 3,3-dimethyl derivative **14b** (phenyl prenyl sulfide) to **16a** and **16b** via the ylides **15a**,**b**,[8] and that of the analogous reaction of *N*-allyl dimethylamine (**17**) to ylide **18** and its subsequent [2,3]sigmatropic rearrangement to **19**[9] according to the procedures reported in the literature. The same chiral Rh(II)-catalysts were screened as above; however, only



Scheme 3.

insignificant levels of induction could be observed. The highest ee of 10% resulted from the reaction of **14a** with [Rh_2{(*S*)-dosp}$_4$] (Scheme 3).

3. Conclusion

The enantioselectivities resulting from diazo decomposition of ethyl 1,1,1-trifluoro-2-diazopropionate (**1**) are less satisfactory than those obtained with other disubstituted carbenes such as vinyl- or phenyl-2-diazoacetates. This low enantioselectivity for olefin cyclopropanation with **1** may be ascribed to the strong electron-attracting effect of the trifluoromethyl substituent. This increases the electrophilicity of the carbene, which results in a higher reactivity. Davies has shown that carbonylcarbenes carrying an electron-donating substituent have later transition states for cyclopropanation, as deduced from their Hammett reaction constant, and these carbenes are also more enantioselective than those carrying electron withdrawing substituents.[25] There seems to be analogy with 2-diazocyclohexane-1,3-diones, which exhibit equally poor enantioselectivities in diazo decompositions.[26] Other types of catalysts may be required to overcome these difficulties. The absence of enantioselectivity in the reactions proceeding via ylides, in turn, may be attributed to dissociation of the ylide from the catalyst.[27]

4. Experimental

General. See Ref. 28. The origin of the chiral Rh(II)-catalysts is indicated in previous publications.[29]

4.1. Cyclopropanation with ethyl 3,3,3-trifluoro-2-diazopropionate (1)

General procedure. The diazo compound **1** (92 mg, 0.50 mmol) in CH_2Cl_2 (5.0 mL) was added to the olefin (5.0 mmol) in CH_2Cl_2 (5.0 mL) containing the appropriate catalyst (5 mol%) within 8 h at room temperature. After completion of the reaction, the mixture was passed through a short plug of silica gel, which was subsequently washed with CH_2Cl_2 (20 mL). The solvent was removed in vacuo, and the crude product was purified by flash chromatography.

4.1.1. Ethyl 1-trifluoromethyl-2,2-diphenyl-cyclopropane-1-carboxylate (3). Yield 55%, mp 108–110 °C. $[\alpha]_D^{20}$=+2.6 (*c*=1.0, $CHCl_3$ for 42% ee with [Rh_2{(*S*)-dosp}$_4$]). IR (film): 3063w, 1725s, 1450m, 1372s, 1255m. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.99 (t, *J*=7.25 Hz, 3H); 2.23 (d, *J*=5.7 Hz, 1H); 2.49–2.52 (m, 1H); 3.85–4.05 (m, 2H); 7.16–7.55 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 13.6 (q); 19.9 (t); 39.2 (q); 44.5 (s); 61.8 (t); 125.0 (q); 127.4–130.2 (10 d); 141.0 (s); 139.2 (s); 165.7 (s). ^{19}F NMR (470 MHz, $CDCl_3$): +103 (C_6F_6). MS: 334 (M^+, 6), 305 (41), 241 (15), 221 (15), 192 (10), 191 (28), 183 (26), 165 (37), 105 (34), 77 (14). HR MS: 334.1170 ($C_{19}H_{17}F_3O_2^+$; calcd 334.1181). Enantiomer separation by HPLC, OD-H column, hexane/isopropanol 99:1.

4.1.2. Ethyl 2-butyl-1-trifluoromethylcyclo-prop-2-en-1-carboxylate (5). For yield and ee: see Table 1. Liquid. $[\alpha]_D^{20}$=−1.6 (*c*=1.0, $CHCl_3$, for 51% ee with [Rh_2{(*S*)-nttl}$_4$]). IR (film): 1733s, 1438w, 1267m, 1146m. ^{1}H NMR ($CDCl_3$, 500 MHz): 0.91 (t, *J*=7.2 Hz, 3H); 1.27 (t, *J*=7.3 Hz, 3H); 1.35–1.42 (m, 4H); 1.52–1.59 (m, 2H); 2.48–2.51 (m, 2H); 4.12–4.30 (m, 2H); 6.28–6.29 (m, 1H). ^{13}C NMR ($CDCl_3$, 500 MHz): 13.6 (q); 14.1 (q); 22.1 (t); 23.4 (t); 28.4 (t); 31.2 (q); 61.3 (t); 91.9 (d); 113.5 (s); 124.0 (q); 179.0 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −65 ($CFCl_3$). MS: 236 (M^+, abs.) 166 (12), 165 (100), 163 (81), 146 (21), 145 (47), 121 (11), 115 (10), 107 (18), 101 (14), 80 (12), 55 (18). HR MS: 208.0712 ($C_9H_{11}F_3O_2^+$; calcd 208.0711). Enantiomer separation by GC, β-Dex, 80 °C, τ_1=29.1, τ_2=29.7 min.

4.1.3. Ethyl 2-cyclohexyl-3,3,3-trifluoropropanoate (7). IR (film): 2930m, 1745s, 1450m, 1261s, 1238s, 1158s, 1127m, 1104s. ^{1}H NMR (500 MHz, $CDCl_3$): 1.03–1.12 (m, 1H); 1.12–1.20 (m, 2H); 1.23–1.32 (m, 2H); 1.30 (t, *J*=5.8 Hz, 3H); 1.63–1.72 (m, 2H); 1.71–1.80 (m, 2H); 1.85–1.93 (m, 1H); 1.95–2.04 (m, 1H); 2.93 (quint. *J*=7.0 Hz, 1H); 4.18–4.28 (dq, *J*=5.8, 1.2 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 14.1 (q); 25.8 (t); 30.4 (t); 30.8 (t); 36.1 (d); 56.3 (q); 61.4 (t); 125 (q); 167.5 (s). ^{19}F NMR (400 MHz, $CDCl_3$, $CFCl_3$): −64. MS: 239 (M^++1, 1), 238 (M^+, <1), 193 (11), 157 (36), 156 (100), 129 (27), 128 (71), 108 (22), 83 (64), 82 (49), 81 (18), 67 (37), 55 (33), 54 (15). HR MS: 239.1279 ($C_{11}H_{18}O_2F_3^+$; calcd 239.1259); 238.1160 ($C_{11}H_{17}O_2F_3^+$; calcd 238.1181).

4.1.4. *cis*/*trans*-Ethyl 1-trifluoromethyl-2-phenylcyclopropane-1-carboxylate (9a). For yields, diastereomer ratio and ee's: see Table 2. Separation of diastereoisomers by flash chromatography (SiO_2, CH_2Cl_2/pentane 10:90). Enantiomer separation by GC (β-Dex, 120 °C).

cis-**9a**. Oil. IR (film): 3028w, 2985w, 1728s, 1383m, 1293s, 1222s, 1156s. ^{1}H NMR ($CDCl_3$, 400 MHz): 1.34–1.36 (t, *J*=7.3 Hz, 3H); 1.91–1.97 (m, 2H); 3.06–3.09 (t, *J*=9.0 Hz, 1H); 4.23–4.29 (m, 2H); 7.18–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): 14.0, (q); 16.1 (t); 32.2 (d); 34 (q); 62.0 (t); 128.1 (d); 129.0 (d); 129.1 (q); 129.4 (d); 133.4 (s); 168.3 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −61.1 ($CFCl_3$). MS: 258 (41), 238 (27), 213 (13), 210 (18), 193 (43), 192 (26), 190 (42), 185 (63), 184 (16), 183 (21), 181 (10), 173 (15), 170 (47), 166 (20), 165 (87), 164 (34), 147 (14), 146 (77), 145 (26), 135 (25), 134 (11), 133 (23), 116 (30), 115 (100), 107 (28), 105 (16), 104 (17), 91 (29), 89 (20), 79 (13), 78 (13), 77 (21), 65 (19), 63 (18), 51 (22). HR MS: 258.0869 ($C_{13}H_{13}F_3O_2^+$; calcd 258.0868).

trans-**9a**. Oil. IR (film): 2984w, 1737s, 1454w, 1373m, 1316m, 1334m, 1198m, 1225m, 1147s, 1229m, 1079m. ^{1}H NMR ($CDCl_3$, 400 MHz): 0.84–0.87 (t, *J*=7.4 Hz, 3H); 1.77–1.80 (m, 1H); 2.13–2.15 (m, 1H); 2.91–2.95 (t, *J*=9.0 Hz, 1H); 3.78–3.89 (m, 2H); 7.10–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): 13.6, (q); 14.9 (t); 29.0 (d); 34.1 (q); 61.4 (t); 123.0 (q); 128.1 (d); 129.0 (d); 133.4 (s); 165.0 (s). ^{19}F NMR (282 MHz, $CDCl_3$): −66.8 ($CFCl_3$). MS: 258 (M^+, 46); 238 (30), 213 (13), 210 (22), 193 (43), 210 (22), 193 (43), 192 (30), 190 (45), 186 (10), 185 (76), 184 (16), 183 (23), 181 (12), 173 (16), 171 (10), 170 (49), 166 (23), 165 (95), 164 (34), 147 (13), 146 (71), 145 (25), 135 (33), 134 (10), 133 (21), 127 (20), 123 (10), 116 (31), 115 (100),

107 (36), 105 (16), 104 (17), 91 (23), 89 (22), 79 (15), 78 (13), 77 (22), 65 (15), 63 (19), 51 (24). HR MS: 258.08670 ($C_{13}H_{13}O_2F_3^+$; calcd 258.0868).

4.1.5. *cis/trans*-Ethyl 2-(4-chlorophenyl)-1-trifluoromethylcyclopropane-1-carboxylate (9b). For yield and ee: see Table 4. IR (film): 2985, 1731, 1373, 1288, 1190. MS: 294 (M^+, 19), 292 (56), 274 (12), 272 (35), 247 (17), 246 (15), 244 (36), 229 (13), 228 (13), 227 (37), 226 (37), 224 (36), 221 (19), 218 (10), 217 (22), 215 (11), 209 (34), 206 (13), 204 (38), 199 (20), 186 (11), 184 (18), 183 (49>), 182 (25), 181 (11), 180 (29), 171 (13), 169 (42), 167 (10), 165 (67), 165 (67), 164 (100), 163 (27), 161 (22), 151 (19), 150 (11), 149 (37), 145 (50), 143 (21), 139 (20), 138 (26), 133 (42), 127 (11), 125 (32), 123 (18), 116 (12), 115 (98), 114 (18), 113 (15), 103 (18), 101 (12), 99 (10), 89 (47), 77 (29), 75 (29), 73 (10), 69 (16), 63 (41), 62 (14), 57 (10), 51 (23), 50 (16). HR MS: 292.0478 ($C_{13}H_{12}F_3O_2^{35}Cl^+$; calcd 292.0478). Enantiomer separation by GC (β-Dex, 120 °C, isothermal).

cis-**9b**. ^{1}H NMR (500 MHz, $CDCl_3$): 1.34–1.36 (t, J=7.3 Hz, 3H); 1.87–1.90 (dd, J=5.4, 5.2 Hz, 1H); 1.93–1.98 (m, 1H); 3.02–3.05 (t, J=9.0 Hz, 1H); 4.26–4.35 (q, J=7.3 Hz, 2H); 7.18–7.35 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.0 (q); 16.2 (t); 31.8 (d); 33.0 (q); 62.2 (t); 125.5 (q); 128.5 (d); 130.8 (d); 132.0 (s); 133.6 (s); 168.0 (s). ^{19}F NMR (280 MHz, $CDCl_3$): −61.0 ($CFCl_3$).

trans-**9b**. ^{1}H NMR (500 MHz, $CDCl_3$): 0.95–0.98 (t, J=7.2 Hz, 3H); 1.76–1.82 (dd, J=7.7, 6.3 Hz, 1H); 2.13–2.16 (m, 1H); 2.89–2.92 (t, J=8.9 Hz, 1H); 3.92–3.96 (q, J=7.2 Hz, 2H); 7.16–7.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): 13.7 (q); 15.1 (t); 28.5 (d); 34.4 (q); 61.6 (t); 125.1 (q); 128.4 (d); 130.5 (d); 132.2 (s); 133.5 (s); 164.9 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −66.9 ($CFCl_3$).

4.1.6. *cis/trans*-Ethyl 2-(4-methoxyphenyl)-1-trifluoromethylcyclopropane-1-carboxylate (9c). IR (film): 2936, 1731, 1612, 1512, 1465, 1372, 1289. MS: 288 (M^+, 57), 268 (32), 259 (11), 243 (14), 223 (17), 222 (12), 216 (14), 215 (100), 214 (22), 213 (24), 200 (16), 195 (35), 180 (15), 165 (17), 151 (10), 145 (17), 135 (13), 134 (13), 121 (10), 103 (11), 91 (11), 77 (14). HR MS: 288.0984 ($C_{14}H_{15}O_3F_3^+$; calcd 288.0973). Enantiomer separation: GC (β-Dex, 120 °C, isothermal).

cis-**9c**. ^{1}H NMR (500 MHz, $CDCl_3$): 1.33–1.36 (t, J=7.3 Hz, 3H); 1.91–1.96 (dd, J=5.4, 5.2 Hz, 1H); 1.88–1.91 (m, 1H); 3.01–3.05 (t, J=9.0 Hz, 2H); 3.80 (s, 3H); 4.26–4.35 (m, 2H); 6.75–7.25 (m, 4H). ^{13}C NMR (125 MHZ, $CDCl_3$): 14.0 (q); 15.6 (t); 31.7 (d); 34.1 (q); 55.3 (d); 61.8 (t); 113.7 (d); 126.0 (q); 129.6 (s); 130.5 (d); 159.0 (s); 168.0 (s). ^{19}F NMR (280 MHz, $CDCl_3$): −61.0, $CFCl_3$).

trans-**9c**. ^{1}H NMR (500 MHz, $CDCl_3$): 0.94–0.96 (t, J=7.2 Hz, 3H); 1.73–1.78 (dd, J=5.6, 5.7 Hz, 1H); 2.10–2.15 (m, 1H); 2.88–2.91 (t, J=8.5 Hz, 1H); 3.79 (s, 3H); 3.89–3.94 (m, 2H); 6.75–7.25 (m, 4H). ^{13}C NMR (500 MHz, $CDCl_3$): 13.8 (q); 15.0 (t); 28.6 (d); 34.0 (q); 55.3 (q); 61.4 (t); 113.6 (d); 125.6 (q); 130.2 (d); 165.2 (s). ^{19}F NMR ($CDCl_3$): −66.6 ($CFCl_3$).

4.1.7. *cis/trans*-Ethyl 1-trifluoromethyl-2-propylcyclopropane-1-carboxylate (9d). IR ($CHCl_3$): 2964m, 1727s, 1374s, 1325s, 1223s, 1150s. MS: 225 (M^++1, 13), 224 (M^+<1), 194 (17), 174 (16), 165 (100), 151 (14), 149 (99), 146 (10), 145 (56), 128 (20), 127 (11), 109 (12), 108 (10), 107 (33), 99 (15), 85 (56), 79 (12), 71 (16), 69 (44), 67 (12), 57 (21), 55 (10). HR MS: 224.1024 ($C_{10}H_{15}O_2F_3^+$; calcd 224.1024). Enantiomer separation: GC (β-Dex, 60 °C, isothermal).

cis-**9d**. ^{1}H NMR 0.94–0.97 (t, J=7.0 Hz, 3H); 1.32–1.33 (t, J=7.2 Hz, 3H); 1.57–1.71 (m, 6H); 1.60–1.75 (m, 1H); 4.25–4.31 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.5 (q); 14.5 (q); 18.0 (t); 22.0 (t); 25.0 (t); 29.0 (d); 31.0 (q); 61.5 (t); 126 (q); 168.9 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −60.5 ($CFCl_3$).

trans-**9d**. ^{1}H NMR (500 MHz, CDC_3): 0.86–0.94 (t; J=7.0 Hz, 3H); 1.28–1.31 (t, J=7.2 Hz, 3H); 1.34–1.55 (m, 6H); 1.59–1.66 (m, 1H); 4.15–4.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.5 (q); 14.1 (q); 17.2 (t); 22.2 (t); 25.7 (d); 28.5 (t); 31.5 (q); 61.6 (t); 124 (q); 166.9 (s). ^{19}F NMR (280 MHz, $CDCl_3$): −66.6 ($CFCl_3$).

4.1.8. *cis/trans*-Ethyl 2-acetoxy-1-trifluoromethylcyclopropane-1-carboxylate (9e). Inseparable mixture of stereoisomers. IR ($CHCl_3$): 2987w, 1761s, 1371s, 1304m, 1239s. MS: 241 (M^++1, 5), 240 (M^+, abs.) 198 (40), 180 (11), 169 (100), 153 (11), 152 (38), 141 (77), 133 (25), 123 (50), (d); 62.4 (t); 124 (q); 166.3 (s); 170.4 (s). MS: 241 (M^++1, 5), 240 (M^+, abs.), 198 (40), 180 (11), 169 (100), 153 (11), 152 (38), 141 (77), 133 (25), 123 (50), 121 (55), 105 (20), 101 (69), 95 (15), 73 (18), 71 (11), 69 (18), 57 (21), 45 (32). HR MS: 241.0681 ($C_9H_{12}O_4F_3^+$; calcd 241.0688). Enantiomer separation: GC (β-Dex, 60 °C, isothermal).

cis-**9e**. ^{1}H NMR (500 MHz, $CDCl_3$): 1.31 (t, J=7.3 Hz, 3H); 1.85–1.89 (m, 1H); 1.89–1.94 (m, 1H); 2.10 (s, 3H); 4.21–4.28 (m, 2H); 4.58–4.64 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 14.0 (q); 16.7 (t); 20.5 (q); 31 (q); 56.5 (d); 56.5 (d); 62.4 (t); 124 (q); 166.3 (s); 170.5 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −61.6 ($CFCl_3$).

trans-**9e**. ^{1}H NMR (500 MHz, $CDCl_3$): 1.31 (t, J=7.3 Hz, 3H); 1.71–1.75 (m, 1H); 2.06–2.08 (m, 1H); 2.10 (s, 3H); 4.20–2.32 (m, 2H); 4.46–4.50 (m, 1H). ^{13}C NMR (500 MHz, $CDCl_3$): 13.9 (q); 16.4 (t); 20.5 (q); 32 (q); 54.0 (d); 62.2 (t); 124 (q); 163.8 (s); 170.3 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −66.2 ($CFCl_3$).

4.2. Hydrolysis of 9a

4.2.1. *cis*-2-Phenyl-1-trifluoromethylcyclopropane-1-carboxylic acid *cis*-10. A 40:60 mixture of *cis*- and *trans*-**9a** (420 mg, 1.63 mmol) was hydrolyzed with KOH (183 mg, 3.3 mmol) in MeOH (15 mL) by stirring overnight at room temperature. The solvent was evaporated, the residue treated with HCl (1 N) and extracted with CH_2Cl_2. Recrystallization (CH_2Cl_2/pentane) afforded *cis*-**10a** (280 mg, 75%), mp 122 °C. IR (film): 3033w, 2870w, 1697s, 1440s, 1368m, 1295s, 1145s, 1120s. ^{1}H NMR (500 MHz, $CDCl_3$): 2.05–2.07 (m, 2H); 3.23–3.26 (m, 1H); 7.31–7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 16.9 (t);

32.6 (q); 32.8 (d); 123 (q); 127.9 (d); 128.4 (d); 129.4 (d); 132.8 (s); 174.4 (s). ^{19}F NMR (470 MHz, $CDCl_3$); −61.5 ($CFCl_3$). MS: 230 (M+, 38), 210 (20), 190 (19), 185 (53), 176 (12), 173 (12), 170 (12), 166 (14), 165 (58), 164 (26), 147 (13), 146 (60), 145 (16), 117 (50), 116 (29), 115 (100), 114 (12), 107 (68), 105 (13), 91 (25), 90 (10), 89 (27), 79 (20), 78 (11), 77 (25), 75 (10), 65 (14), 63 (26), 51 (32), 50 (12). HR MS: 230.0557 ($C_{11}H_9O_2F_3^+$; calcd 230.0555).

4.2.2. *trans*-2-Phenyl-1-trifluoromethylcyclopropane-1-carboxylic acid, *trans*-10. The ester *trans*-**9a** (34 mg, 0.13 mmol) was hydrolyzed with KOH (15 mg, 0.27 mmol) in MeOH (1.5 mL) at 50 °C during 24 h. Work-up as above afforded *trans*-**10** (19 mg, 62%) as yellowish oil. IR (film): 3030w, 2923m, 2623w, 1698s, 1462m, 1432m, 1393m, 1317s, 1222m, 1240m, 1125s, 1148s, 1079s, 953m, 894m, 787m. ^{1}H NMR (500 MHZ, $CDCl_3$): 1.82–1.85 (m, 1H); 2.12–2.14 (m, 1H); 3.02–3.04 (m, 1H); 7.30–7.40 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 15.8 (t); 30.3 (d); 33.8 (q); 124 (q); 127.8 (d); 128.3 (d); 129.0 (d); 132.9 (s); 169.1 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −66.9 ($CFCl_3$). MS: 230 (M^+, 37), 210 (21), 190 (19), 185 (53), 173 (12), 170 (11), 166 (13), 165 (58), 164 (26), 147 (14), 146 (61), 145 (16), 134 (10), 133 (17), 117 (14), 116 (29), 115 (100), 114 (13), 107 (78), 91 (24), 90 (12), 89 (28), 79 (25), 78 (13), 76 (10), 75 (11), 65 (18), 63 (33), 62 (11), 51 (41), 50 (16). HR MS: 230.0558 ($C_{11}H_9O_2F_3^+$; calcd 230.0555).

4.2.3. *p*-Bromophenacyl *cis*-2-phenyl-1-trifluoromethyl-cyclopropane-1-carboxylate *cis*-11. To the acid *cis*-**10** (140 mg, 0.61 mol) in toluene (15 mL) was added DBU (93 mg, 0.61 mmol), followed by *p*-bromophenacyl bromide (170 mg, 0.61 mmol). The mixture was stirred at room temperature for 90 min, whereupon it was hydrolyzed with H_2O (3.0 mL). The organic layer was filtered through celite, washed with satd. $NaHCO_3$ and HCl (1 N), and evaporated. The residue was purified by flash chromatography (SiO_2, ether/pentane 20:80) and recrystallized from ether/pentane to afford *cis*-**11** (75 mg, 29%) as colorless crystals, mp 98–99 °C. IR (film): 2947w, 1740s, 1703s, 1588m, 1373s, 1296s, 1220s, 1142s. ^{1}H NMR (500 MHz, $CDCl_3$): 2.03–2.07 (m, 1H); 2.07–2.13 (m, 1H); 3.27–3.30 (m, 1H); 5.35–5.53 (m, 2H); 7.28–7.38 (m, 5H); 7.66–7.69 (m, 2H); 7.78–8.02 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): 16.3 (t); 32.9 (d); 66.7 (t); 127.8 (d); 128.4 (d); 129.3 (d); 129.5 (d); 132.4 (d); 132.2 (q); 133.2 (s); 166.0 (s); 190.5 (s). ^{19}F NMR (470 MHz, $CDCl_3$): −61.2 ($CFCl_3$). MS: 428 (M^+, 4), 213 (11), 212 (82); 193 (25), 192 (96), 185 (98), 184 (25), 183 (100), 174 (10), 171 (11), 169 (12), 164 (10), 157 (22), 116 (10), 115 (34), 104 (16), 90 (12), 89 (10), 76 (20), 75 (14), 50 (11). HR MS: 426.0071 ($C_{19}H_{14}O_3F_3^{79}Br^+$; calcd 426.0078); 428.0066 ($C_{19}H_{14}O_3F_3^{81}Br^+$; calcd 428.0058).

4.3. X-ray structure of *p*-bromophenacyl *cis*-2-phenyl-1-trifluoromethylcyclopropane-1-carboxylate (*cis*-11)

$C_{19}H_{14}BrF_3O_3$; M_r=427.2; μ=2.375 mm^{-1}, d_x=1.608 g cm^{-3}, monoclinic, $P2_1/n$, Z=4, a=9.4115(5) Å, b=18.9344(12) Å, c=9.9426(7) Å, β=94.984(8)°, V=1765.1(2) Å^3; cell dimensions and intensities were measured at 200 K on a Stoe IPDS diffractometer. Full-matrix least-squares refinement based on F using weight of $1/(\sigma^2(F_o)+0.00015(F_o^2))$ gave final values $R=\omega R=0.030$ and S=1.03(1) for 235 variables and 1863 contributing reflections.

Crystallographic data (excluding structure factors) for *cis*-**11** have been deposited to the Cambridge Crystallographic Data Base as supplementary publication number CCDC-226786. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. +44-1223-336-033;e-mail: deposit@ccdc.cam.ac.uk).

4.3.1. Reduction of 9a. *cis*/*trans*-2-Trifluoro-methyl-2-hydroxymethyl-2-phenylcyclopropane (12). The ester **9a** (72 mg, 0.28 mmol of *cis*/*trans*-mixture) in THF (2.0 mL) was added by syringe to $LiAlH_4$ (19 mg, 0.5 mmol) in THF in 30 min at 0 °C. After the addition, the mixture was heated to reflux for 4 h. AcOEt was added to decompose remaining $LiAlH_4$, followed by water. After extraction with Et_2O, the organic layer was filtered through a plug of silica gel, which was washed with AcOEt.(20 mL). The solvent was removed, and the crude product purified by flash chromatography. Yield 43 mg (71%) as *cis*/*trans* mixture, which was separated by flash chromatography (SiO_2, CH_2Cl_2/pentane 60:40).

cis-**12**. IR (film): 3630w, 1387w, 1211m, 1213m, 1220s, 1136m. ^{1}H NMR (500 MHz, $CDCl_3$): 1.25–1.33 (m, 1H); 1.63–1.67 (m, 1H); 2.58–2.59 (t, J=7.7 Hz, 1H); 3.75 (d, J=13 Hz, 1H); 4.01 (d, J=13 Hz, 1H); 7.22–7.23 (m, 5H). ^{13}C NMR 125 MHz, $CDCl_3$): 11.4 (t); 26.7 (d); 31.8 (q); 64.7 (t); 125.0 (q); 126.9 (d); 128.1 (d); 129.3 (d); 134.9 (s). ^{19}F NMR (300 MHz, $CDCl_3$); −63.1 ($CFCl_3$). MS: 216 (M^+, 14), 198 (22), 186 (18), 185 (16), 166 (16), 165 (25), 164 (11), 130 (11), 129 (100), 128 (16), 117 (21), 116 (10), 115 (24), 107 (15), 104 (14), 91 (26), 89 (10), 78 (13), 77 (14), 63 (10), 51 (15). HR MS: 216.0784 ($C_{11}H_{11}OF_3^+$; calcd 216.0762).

trans-**12**. IR (film): 3030w, 2923w, 1698s, 1431m, 1393m, 1317s, 1239m, 1221m, 1148s, 1125s, 1079s. ^{1}H NMR (500 MHz, $CDCl_3$): 1.37–1.41 (m, 1H); 1.46–1.51 (m, 1H); 2.74–2.78 (t; J=9.0 Hz, 1H); 3.50 (d, J=12.5 Hz, 1H); 3.62 (d, J=12.5, 1H); 7.19–7.27 (m, 5H). ^{13}C NMR 125 MHz, $CDCl_3$): 11.1 (t); 24.9 (d); 30.7 (q); 60.4 (t); 125 (q); 127.5 (d); 128.7 (d); 128.9 (d); 134.8 (s). ^{19}F NMR 380 MHz, $CDCl_3$): −69.1 ($CFCl_3$). MS: 216 (15, M^+), 198 (26), 186 (21), 185 (19), 166 (19), 165 (25), 164 (10), 130 (12), 129 (100), 128 (16), 117 (21), 116 (11), 115 (23), 107 (16), 104 (15), 91 (18), 89 (10), 78 (14), 77 (15), 63 (10), 51 (16). HR MS: 216.0766 ($C_{11}H_{11}OF_3^+$; calcd 216.0762).

The alcohol *trans*-**12** was also obtained in 60% yield upon reduction of the ester *trans*-**9a** with $LiAlH_4$ in THF as colorless solid after purification by flash chromatography (SiO_2, CH_2Cl_2/pentane 55:45).

4.4. Rh(II)-catalyzed decomposition of 1 in the presence of allyl phenyl sulfides

General procedure. The allyl phenyl sulphide (1.00 mmol) and $[Rh_2(OAc)_4]$ (0.05 mmol) was stirred in benzene

(5.0 mL) until the solution was homogeneous. Ethyl 1,1,1-trifluoro-2-diazopropionate (**1**, 1.10 mmol) was added at once, and the mixture was stirred and heated until gas evolution ceased. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, pentane/CH_2Cl_2 60:40) to afford **16a**,**b**.

4.4.1. Ethyl 2-trifluoromethyl-2-phenylthio-pent-4-enoate (16a). Yield 45%, liquid. IR (neat): 3087w, 2986w, 2928w, 1737s, 1441w, 1474w, 1369w, 1322m, 1266s. ^{1}H NMR (500 MHz, $CDCl_3$): 1.15 (t, J=7.0 Hz, 3H); 2.68–2.73 (m, 1H); 2.87–2.91 (m, 1H); 3.97–4.10 (m, 2H); 5.13–5.21 (m, 2H); 5.75–5.88 (m, 1H); 7.32–7.44 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.7 (q); 37.2 (t); 61. (q); 62.2 (t); 119.7 (t); 124 (q); 128.8 (d); 130.4 (d); 131.1 (d); 131.7 (d); 133.6 (s); 142.0 (d); 165.6 (s). ^{19}F NMR (300 MHz, $CDCl_3$, $CDCk_3$): −66.1 ($CFCl_3$). MS: 304 (M^+, 27), 231 (16), 217 (15), 189 (38), 148 (14), 147 (10), 136 (43), 135 (17), 110 (60), 109 (100), 77 (13), 65 (23), 51 (10). HR MS: 304.0752 ($C_{14}H_{15}O_2SF_3^+$; calcd 304.0745). Enantiomer separation: GC (γ-dex, 80–120 °C).

4.4.2. Ethyl 2-trifluoromethyl-3,3-dimethyl-2-phenylthiopent-4-enoate. With phenyl prenyl sulfide. Yield 55%, liquid. IR (neat): 2977w, 1734s, 1472w, 1246s, 1142s, 1025m, 916m. ^{1}H NMR (500 MHz, $CDCl_3$): 1.23 (t, J=7.2 Hz, 3H); 1.39 (s, 3H); 1.45 (s, 3H); 4.04–4.24 (m, 2H); 5.10–5.18 (m, 2H); 6.17–6.23 (M, 1H); 7.27–7.62 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 13.9 (q); 24.4 (q); 26.0 (q); 43.7 (s); 62.5 (t); 72 (q); 113.3 (t); 124 (q); 128.6 (d); 129.7 (d); 130.0 (s); 137.1 (d); 142.8 (d); 165.9 (s). ^{19}F NMR (470 MHz, $CDCl_3$): +96 (C_6F_6). MS: 332 (M^+,1), 264 (41), 109 (23), 70 (10), 69 (100). HR MS: 332.1023 ($C_{16}H_{19}SFO_2^+$; calcd 332.1058).

4.5. Rh(II)-catalyzed decomposition of 1 in the presence of *N*-allyldimethylamine (17)

4.5.1. Ethyl 2-trifluoromethyl-2-*N*,*N*-dimethylamino pent-4-enoate (19). *N*-Allyldimethylamine (**17** 1.00 mmol) and [$Rh_2(OAc)_4$] (0.05 mmol) in dry benzene (5.0 mL) was stirred until the solution was homogeneous. Ethyl 2,2,2-trifluoro-2-diazopropionate (**1**, 1.0 mmol) was added at once, and the mixture was stirred and heated until gas evolution ceased. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (SiO_2, pentane CH_2Cl_2) 1:1 to afford **19** (60%) as liquid. IR (neat): 2926m, 1742s, 1460m, 1174s. ^{1}H NMR 500 MHz, $CDCl_3$): 1.32 (t, J=7.3 Hz, 3H); 2.51 (s, 3H); 2.52 (s, 3H); 2.74 (d, J=7.2 Hz, 2H); 4.23.4.32 (m, 2H); 5.14–5.18 (m, 2H); 5.77–5.84 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): 14.0 (q); 36.3 (t); 40.0 (s); 61.9 (t); 72.0 (q); 119.5 (t); 125 (q); 130.9 (d), 167.9 (q). ^{19}F NMR (470 MHz, $CDCl_3$): +98 (C_6F_6); −66.4 ($CFCl_3$). MS: 239 (M^+, 2), 198 (27), 170 (20), 150 (10). HR MS: 239.1100 ($C_{10}H_{16}NF_3O_2^+$; calcd 239.1133).

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Identification of a dehydrodimer of avenanthramide phytoalexin in oats

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Abstract—A new compound (**1**) was found to accumulate when oat leaves were treated with elicitors. A reaction with peroxidase and avenanthramide B, an oat phytoalexin, in the presence of hydrogen peroxide resulted in the formation of **1**. The chemical structure of **1** was determined to be a cyclic dehydrodimer of avenanthramide B based on spectroscopic analyses and chemical derivatization, and **1** was named bisavenanthramide B.

1. Introduction

Plants respond to pathogens by accumulating low molecular-weight antimicrobial compounds, phytoalexins. Oat (*Avena sativa*) leaves produce a series of hydroxycinnamic acid amides with hydroxyanthranilates, avenanthramides, as phytoalexins upon infection by phytopathogenic fungi.[1,2] The production of avenanthramides is also evoked by the treatment of leaves with elicitors, such as oligo-*N*-acetylchitooligosaccharides,[3] a host-specific toxin victorin C,[4] and heavy metal ions.[5] Oligomeric compounds of phenolics have been found in plant kingdom, and some of them have been suggested to play a role in interactions between plants and micoroorganisms.[6–8] Since avenanthramides are a characteristic constituent of oats, their oligomers would have novel structures. In the present study, a new dimerized avenanthramide was found to accumulate when oat leaves were treated with elicitors, and its chemical structure was determined.

2. Results and discussion

Primary leaves from 7-d-old oat seedlings were treated with low molecular weight, partially deacetylated chitin (100 $\mu g\ ml^{-1}$), an effective elicitor of phytoalexin production in oats. After a 72-h incubation, the elicitor solution was analyzed by reversed-phased HPLC, and a new compound (**1**) was found to accumulate along with known oat phytoalexins, avenanthramides A, B, G, and L. The induction of **1** was also observed when the leaves were treated with another elicitor, penta-*N*-acetylchitopentaose (1 mM), but not in the leaves treated with distilled water. In addition, **1** was detected in the leaves 72 h after inoculation with a phytopathogenic fungus, *Bipolaris maydis*, whereas **1** was not detected in healthy leaves. Ion-spray LC/MS analysis revealed the molecular weight of **1** to be 656 on the basis of an $[M+H]^+$ at *m/z* 657. The elicitor solution was subjected to chromatography on an ODS column and then preparative HPLC to afford pure **1**. Since the molecular weight corresponded to that of the dehydrodimer of avenanthramide B, we carried out a reaction with avenanthramide B and peroxidase extracted from elicited oat leaves in the presence of hydrogen peroxide for the large-scale preparation of **1**. The major product of the reaction showed the same retention time on HPLC as **1**. This compound was purified by preparative HPLC, and confirmed to be identical to **1** by comparing ^1H NMR, UV, and ion-spray mass spectra as well as chromatographic behavior on HPLC. We also confirmed that **1** formed in a reaction of avenanthramide B with commercial horseradish peroxidase. For further chemical characterization, we utilized **1** prepared using the enzyme reaction with peroxidase from elicited oat leaves.

Compound **1** had the molecular formula $C_{34}H_{28}N_2O_{12}$ as revealed by HRFABMS (*m/z* 657.1708, $[M+H]^+$), which was consistent with that of a possible dehydrodimer of avenanthramide B. The structure of **1** could not be directly determined from NMR spectra because of intense overlapping of signals on the ^1H NMR spectrum in the aromatic region. We also obtained **1**[*] in a peroxidase reaction with [8′,9′-$^{13}C_2$]avenanthramide B in the presence of hydrogen

Keywords: Avenanthramide; Phytoalexin; Dehydrodimer; Peroxidase; *Avena sativa*.
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peroxide. However, the completely overlapping signals of two carbonyl carbons in the NMR spectra prevented us from determining its structure as well.

To obtain simpler spectra, **1** was hydrolyzed in 1 N HCl. The hydrolysate **2** was obtained as the main product. The molecular formula of **2** was determined to be $C_{27}H_{23}NO_{10}$ on the basis of HRFABMS (*m/z* 522.1396, $[M+H]^+$). Thus, a 5-hydroxyanthranilic acid moiety was removed from **1** by hydrolysis. The release of 5-hydroxyanthranilate was also confirmed by HPLC analysis of the reaction mixture.

Although the molecular formula indicated the presence of 27 carbons in **2**, the ^{13}C NMR spectrum showed 26 signals. Two methoxy carbon signals predicted based on ^1H NMR [δ 3.73 (CH_3O-B3) and 3.86 (CH_3O-D3)] overlapped at δ 56.3 ppm. The multiplicity of carbons was determined in a HMQC experiment. The ^{13}C NMR spectrum showed two methine signals at δ 53.7 and 68.5, corresponding to ^1H NMR signals at δ 4.21 (m, H-3) and 5.33 (d, J=3.6 Hz, H-2), respectively. The ^{13}C NMR spectrum also showed three carbonyl signals (δ_C 168.8, 170.8, and 174.2) and 20 signals in the aromatic region. The ^1H NMR spectrum displayed three groups of typical ABX spin system signals corresponding to 1,2,4-trisubstituted benzene rings: A ring [δ 6.82 (dd, J=8.7, 2.8 Hz, H-A5), 6.91 (d, J=8.7 Hz, H-A6), and 7.33 (d, J=2.8 Hz, H-A3)], B ring [6.71 (d, J=8.1 Hz, H-B5), 6.77 (dd, J=8.1, 1.8 Hz, H-B6), and 6.99 (d, J=1.8 Hz, H-B2)], and D ring [6.83 (d, J=8.2 Hz, H-D5), 7.04 (dd, J=8.2, 1.8 Hz, H-D6), and 7.11 (d, J=1.8 Hz, H-D2)]. Therefore, eighteen of 20 signals in the aromatic region on the ^{13}C NMR spectrum constitute three trisubstituted benzene rings. The remaining one quaternary carbon and one tertiary carbon bearing a proton [δ_H 7.52 (d, J=2.2 Hz, H-1′)] were assigned to a double bond on the basis of the molecular formula and their chemical shifts.

Using a similar protocol to the hydrolysis of **1**, we prepared **2*** from **1*** that had four ^{13}C atoms. The ^{13}C NMR spectrum of **2*** showed four intense signals of enriched ^{13}C atoms at δ_C 53.7 (dd, $^1J_{3-4}$=43.6 Hz, $^1J_{3-6}$=57.9 Hz, C-3), 126.8 (dd, $^1J_{4-3}$=43.6 Hz, $^1J_{4-5}$=64.3 Hz, C-4), 170.8 (d, $^1J_{5-4}$= 64.3 Hz, C-5) and 174.2 (d, $^1J_{6-3}$=57.9 Hz, C-6) ppm. Their homonuclear spin couplings and chemical shifts revealed a substituted 1,4-butadione structure: O═C*–C*H–C*(═CH)–C*═O (*carbon atom labeled with ^{13}C). The COSY spectrum of **2** showed a correlation between H-2 and H-3, and the HMBC spectrum of **2** showed correlations of H-2 with C-3 and C-6, indicating a linkage between C-2 and C-3. Consistent with this structure, a methine signal (δ_H 4.21, m, H-3) in **2*** was further split ($^1J_{HC}$=136 Hz) in **2***, and two doublet signals of the olefinic proton (δ_H 7.52, H-1′) and the other methine proton (δ_H 5.33, d, H-2) in **2** became two multiplets in **2*** with heteronuclear spin coupling.

The trisubstituted benzene rings B and D were determined to be two 3-methoxy-4-oxygenated phenyl groups in HMBC and NOESY experiments (Fig. 1, structure A). The HMBC spectrum displayed correlations of H-2 with C-B2 and C-B6, indicating a connection between C-B1 and C-2. Similarly, in the HMBC spectrum, two aromatic carbons, C-D2 and C-D6, showed cross-peaks with the olefinic proton H-1′, indicating a connection between C-D1 and C-1′. The substitution pattern of the B and D rings indicated that these rings were derived from two ferulic acid units. Therefore, the remaining 1,2,4-trisubstituted benzene ring (A ring) is derived from 5-hydroxyanthranilic acid. Supporting this, the HMBC spectrum showed a correlation between a carbonyl carbon signal (δ_C 168.8) and the proton signal H-A3 (δ_H 7.33) (Fig. 1, structure B).

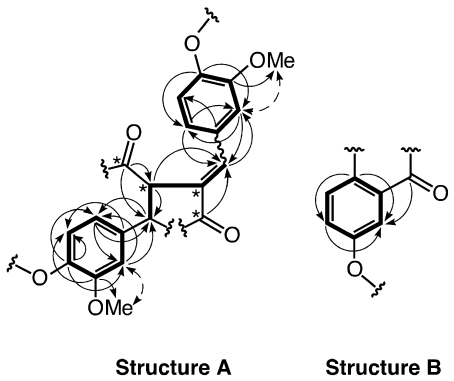


Figure 1. HMBC correlations (indicated by arrows from ^{13}C to ^1H), COSY correlations (indicated by bold lines) and NOESY correlations (indicated by double-headed arrows between protons) for **2**. Critical NOESY correlations used in determining the partial planar structure of **2** are shown. The positions of carbon atoms labeled with ^{13}C in **2*** are indicated by asterisks.

Compound **2** was methylated with (trimethylsilyl)diazomethane to give **3**. HREIMS of **3** gave an $[M]^+$ at *m/z* 591.2112, corresponding to a possible molecular formula of $C_{32}H_{33}NO_{10}$, indicating the introduction of five new methyl groups. The NMR analyses revealed that the partial structure in Figure 1 was conserved in **3**, and that three of the new methoxy groups are linked to C-6, C-B4 and C-D4. In the NOESY spectrum, a methoxy proton signal at δ_H 3.785 showed cross-peaks with aromatic protons, H-A3 (δ_H 7.39) and H-A5 or H-A6 (δ_H 6.85–6.88), indicating the methylation of the hydroxy group at C-A4. In the HMBC spectrum, another methoxy proton signal (δ_H 3.88) displayed a cross-peak with a carbonyl carbon at δ_C 166.4, indicating a methoxycarbonyl group. The methoxycarbonyl carbon showed a correlation to H-A3 (δ_H 7.39). Thus, the methoxycarbonyl group was linked to C-A2 (δ_C 129.5). These observations indicated the presence of a 4-methoxy-2-methoxycarbonylphenyl group (A ring). In

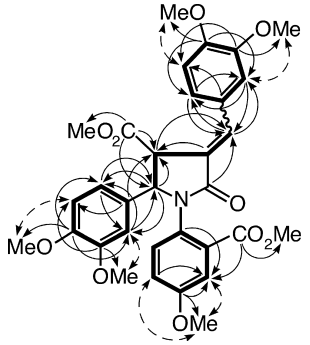


Figure 2. HMBC correlations (indicated by arrows from ^{13}C to ^1H), COSY correlations (indicated by bold lines) and NOESY correlations (indicated by double-headed arrows between protons) for **3**. Critical NOESY correlations used in determining the partial planar structure of **3** are shown.

addition, the assignment of the methoxy groups revealed that all the phenolic hydroxy groups and carboxy groups were methylated. Therefore, these groups were deduced not to be involved in the linkage. Considering the presence of a nitrogen atom in the molecular formula of **3**, the 4-methoxy-2-methoxycarbonylphenyl structure was connected to structure A via a nitrogen atom to form a 5-membered lactam structure as shown in Figure 2.

The proposed structure of **3** had two chiral carbons (C-2 and C-3). Since the NOESY spectrum of **3** displayed correlations of H-3 with H-A6 and H-B2, whereas no correlations were observed between vicinal protons, H-2 and H-3 (Fig. 3), compound **3** has the *trans* configuration of H-2/H-3. The relatively small coupling constant of these protons (J=3.7 Hz) also inferred the *trans* configuration.[9] The double bond of C-4 and C-1′ was suggested to have the *E* configuration, because H-3 showed a correlation with H-D2 and H-D6 but not with H-1′ in the NOESY spectrum.

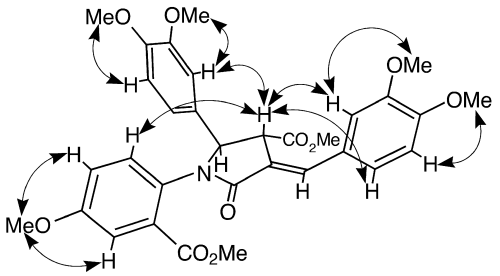
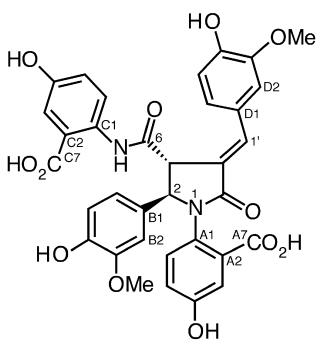
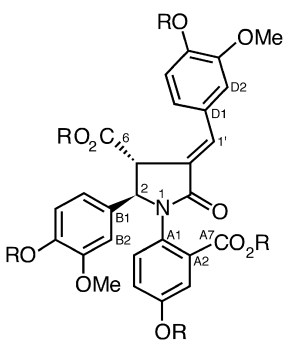


Figure 3. NOESY correlations and relative stereochemistry of **3**.

The NMR signals of **2** were assigned as shown in Table 1 and in the Section 3 on the basis of the assignment of the signals of **3**. The comparison of ^{13}C NMR signals of **1** with those of **2** identified the signals from the 5-hydroxyanthranilic acid released by hydrolysis and the signals from the remaining part of **1**. The low field shift of ^{13}C NMR signals of C-6 and C-3 after hydrolysis indicated the connection of the 5-hydroxyanthranilic acid group to the remaining part of the molecule at C-6. The chemical shifts of the ^{1}H and ^{13}C NMR signals of the 5-hydroxyanthranilic acid part in **1** was almost identical with those in avenanthramide B, indicating that the amide linkage was conserved after the dimerization. The assignments of the NMR signals of **1** were also shown in Table 1 and in Section 3. The relative structures of **1** and **2** were determined based on the NOESY correlations similar to those observed for **3**. The IUPAC name of **1** was 1-(2-carboxy-4-hydroxyphenyl)-*E*-4-(4-hydroxy-3-methoxybenzylidene)-2-(4-hydroxy-3-methoxyphenyl)-5-oxopyrrolidine-3-carbamoyl-5-hydroxyanthranilate. Compound **1** was named bisavenanthramide B.



1



2: R=H
3: R=Me

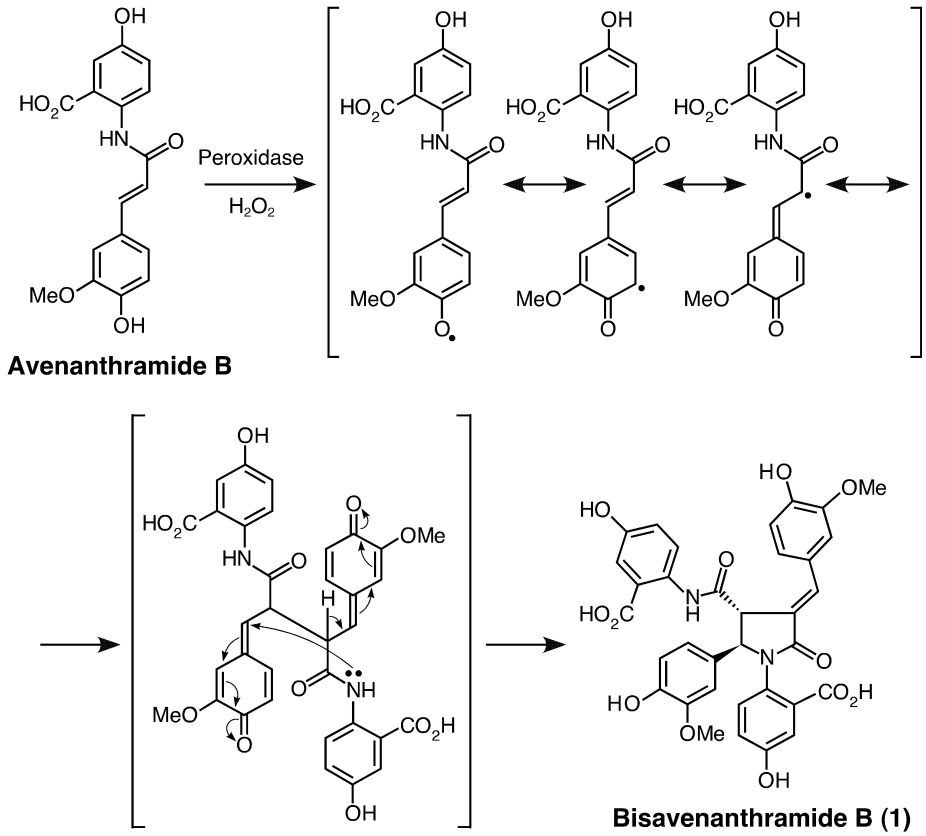
Table 1. ^{13}C NMR spectral data for **1**–**3** (75 MHz, **1** and **2** in MeOH-d_4; **3** in $CDCl_3$)

Carbon	1	2	3
2	69.2	68.5	66.5
3	57.1	53.7	52.46
4	125.9	126.8	125.5
5	170.7[a]	170.8	168.3
6	170.7[a]	174.2	171.4
CH_3O-6			52.7
A1	129.5	129.2	129.2
A2	131.1[b]	131.5	129.5
A3	118.8	118.6	115.7
A4	157.9	157.7	158.0
A5	120.1	120.0	118.2
A6	131.1[b]	130.2	128.1
A7	168.4	168.8	166.4
CH_3O-A4			55.6
CH_3O-A7			52.49
B1	132.8	132.4	132.3
B2	111.8	111.6	109.6
B3	149.4	149.3	149.6
B4	147.9	147.9	149.2
B5	116.3	116.1	111.04[††]
B6	121.7	121.7	119.8
CH_3O-B3	56.4[†]	56.3[c]	56.0
CH_3O-B4			55.8[d]
C1	133.6		
C2	120.4		
C3	118.1		
C4	154.6		
C5	121.6		
C6	123.8		
C7	170.1		
1′	138.2	136.4	135.5
D1	127.6	127.7	127.4
D2	113.5	113.6	112.2
D3	149.1	149.0	148.9
D4	149.7	149.5	150.2
D5	116.5	116.4	110.97[††]
D6	126.3	126.0	123.8
CH_3O-D3	56.3[†]	56.3[c]	55.8[d]
CH_3O-D4			55.9

Signals with the same lower case superscript overlap.
[†,††]Assignments may be interchanged.

The HPLC with a chiral column, CHIRALCEL OD-RH, was effective for the optical resolution of bisavenanthramide B. The analysis of bisavenanthramide B either purified from the elicitor solution or synthesized by peroxidase reaction showed two peaks with an almost identical area, indicating that bisavenanthramide B was a racemic mixture of around 1:1.

A plausible reaction scheme is shown in Scheme 1. First, two phenoxy radicals produced by peroxidase make a covalent bond between C-8′ carbons of two molecules of avenanthramide B. The nucleophilic addition of a nitrogen to a quinone methide from the other avenanthramide B and subsequent tautomerization result in the formation of bisavenanthramide B. The reaction of avenanthramide B with commercial horseradish peroxidase in the presence of hydrogen peroxide also gave bisavenanthramide B, indicating that no other factors are required for the bisavenanthramide formation.



Scheme 1. Plausible reaction scheme for biogenesis of bisavenanthramide B.

Bisavenanthramide B is one of lignanamides, which are lignans possessing at least one amide group.[10] Lignanamides are structurally diverse compounds consisting of acyclic[11–13] and cyclic lignanamides. The latter can be further classified into four categories on the basis of the type of linkages, i.e. arylnaphthalene lignanamide,[6] aryldihydronaphthalene lignanamides,[14,15] dihydrobenzofuran lignanamides,[12,16–21] and tetrahydrofuran lignanamides.[22] Bisavenanthramide B represents a new class of cyclic lignanamides because the butanelactam-type linkage has not been found to the best of our knowledge although the linkages between C-8′ carbons observed in bisavenanthramide B have been found in cannabisins,[6,11,14] jacpaniculines,[22] hyoscyamide[13] and lignanamides from *Porcelia macrocarpa*.[15] We carried out a reaction of avenanthramide B with peroxidase to prepare bisavenanthramide B. Hydroxycinnamic acid amides have been subjected to the reaction with peroxidase for the investigation of lignanamide biosynthesis,[16,17,19] but dimerized amides with a butanelactam-type linkage have not been identified as reaction products. Thus, bisavenanthramide B represents a new reaction sequence initiated by the radical formation catalyzed by peroxidase.

The metabolism of phytoalexins has not been elucidated in detail in comparison with the biosynthesis. However, the metabolism of secondary constituents can be a physiologically important process in plants. For instance, morphine has been demonstrated to be quickly metabolized to bismorphine consisting of two morphine units in response to stress, which results in the cross-linking of polysaccharides in the cell walls in the opium poppy.[23,24] Accumulation of phenolic materials in cell walls in response to infection of pathogens has been shown in various plants including oats.[25] Bisavenanthramides may play a role in the reinforcement of cell walls as a part of phenolic architecture in addition to being a constituent of phytoalexin mixture.

3. Experimental

3.1. General

Melting points were determined with a Yanagimoto micro melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer, and 2-D NMR spectra (COSY, HMQC, HMBC and NOESY) on a Bruker ARX 500 spectrometer with TMS as an internal standard. Positive ion-spray MS were obtained using a Perkin–Elmer–Sciex API-165 mass spectrometer combined with a Shimadzu 10A HPLC system equipped with an ODS column (Mightysil RP-18, 150 mm long, 4.6 mm i.d.). EIMS were obtained with a Shimadzu GCMS-QP5050A mass spectrometer. The HRMS of **1** was obtained with a JEOL MS700 mass spectrometer and those of **2** and **3** with a JEOL JMS-600H mass spectrometer. FABMS were obtained using a glycerol as a matrix. UV spectra were recorded on a Shimadzu UV-2200A spectrophotometer, and IR spectra on a Shimadzu FTIR 8300 spectrophotometer. Optical rotation was recorded with a JASCO DIP 1000 polarimeter. Preparative HPLC was performed using an ODS column (Wakosil II 5C18HG, 250 mm long, 20 mm i.d.) at flow rate of 8.0 ml min^{-1} and a column temperature of 40 °C. Unless stated otherwise, a two-solvent system was

used for HPLC to generate the mobile phase: solvent A, H_2O–TFA (100:0.1); solvent B, MeOH.

3.2. Chemicals

Penta-*N*-acetylchitopentaose and (trimethylsilyl)diazomethane (2.0 M in diethylether) were purchased from Seikagaku Kogyo, Tokyo and Aldrich, respectively. Avenanthramides were synthesized as described previously.[26–28] [$^{13}C_3$]Malonic acid (99 at.% of $^{13}C_3$) was purchased from Isotec, Miamisburg, Ohio. Other chemicals were obtained from Wako Pure Chemical Industries, Osaka.

3.3. Plant materials

Caryopses of oat (*Avena sativa* L. cv. Shokan 1) soaked in distilled water for 12 h at 20 °C were shown in wet vermiculite, and maintained at 20 °C for 7 d under continuous fluorescent light (15 W m^{-2}) in a growth chamber.

3.4. Analysis of elicitor inducible metabolites

Segments (ca. 0.4 g) were taken from the primary leaves of 7-d-old oat seedlings. The lower epidermis was peeled away and the segments were floated on a solution (4 ml) of low molecular weight, partially deacetylated chitin (100 μg ml^{-1}; M_W=3,000–30,000, acethylation rate=50–60%), penta-*N*-acethylchitopentaose (1 mM), or distilled water. After incubation for 48–72 h at 20 °C, the solutions were applied to a Sep-Pak C18 cartridge (waters), and the cartridge was eluted with MeOH–H_2O (90:10). The eluate was concentrated in vacuo, and the residue was dissolved in 400 μl of MeOH, followed by reversed-phase HPLC analysis [column, Mightysil RP-18, 150 mm long, 4.6 mm i.d.; elution, liner gradient B–A (15:85 to 80:20) for 50 min; flow rate, 0.8 ml min^{-1}; detection, 280 nm]. The retention time of **1** was 25.6 min.

3.4.1. Isolation of compound 1 from elicited oat leaves. After the peeling off the lower epidermis, oat leaves (26.7 g) were floated on 3.7 l of 100 μg ml^{-1} partially deacetylated chitin solution. The leaves were incubated for 4 d at 20 °C, and the elicitor solution was collected. After acidification by HOAc (6 ml), the solution was loaded on an ODS column (Cosmosil 75C18-OPN, 50 mm long, 40 mm, i.d., Nacalai Tesque, Kyoto) equilibrated with H_2O–HOAc (100:2). The column was washed with 180 ml of H_2O–HOAc (100:2), and eluted stepwise with 180 ml of each of the mixtures of MeOH–H_2O–HOAc (20:80:2, 40:60:2 and 60:40:2). Compound **1** was eluted in the 40% MeOH fraction. The fraction was concentrated, and subjected to preparative HPLC [eluent, B–A (33:67); detection, 330 nm] to give **1** (rt 53.7 min; yield, 1.2 mg). UV λ_{max} (MeOH) nm (log ε): 204 (4.61), 265 (4.31), 329 (4.45); ion-spray MS *m/z* (rel. int.): 679 $[M+Na]^+$ (28), 657 $[M+H]^+$ (100), 639 $[M+H-H_2O]^+$ (31), 288 (34); ^{1}H NMR (300 MHz, MeOH-d_4): δ 3.73 (3H, s), 3.76 (3H, s), 4.28 (1H, m), 5.33 (1H, d, *J*=3.6 Hz), 6.73 (1H, d, *J*=8.1 Hz), 6.75–6.90 (4H, overlapping signals), 6.94 (1H, dd, *J*=9.0, 3.0 Hz), 6.99 (1H, bs), 7.04 (1H, dd, *J*=8.3, 1.7 Hz), 7.07 (1H, d, *J*=1.7 Hz), 7.36 (1H, d, *J*=2.7 Hz), 7.38 (1H, d, *J*=3.0 Hz), 7.69 (1H, d, *J*=2.2 Hz), 8.23 (1H, d, *J*=9.0 Hz).

3.4.2. Preparation of [8,9-$^{13}C_2$]ferulic acid. [8,9-$^{13}C_2$]-Ferulic acid was synthesized from [$^{13}C_3$]malonic acid (139.4 mg) and vanillin (228 mg) using a protocol described previously[29] (yield 79.1 mg, 30.8%). EIMS 70 eV *m/z* (rel. int.): 196 $[M]^+$ (100), 181 $[M-CH_3]^+$ (23); ^{1}H NMR (300 MHz, MeOH-d_4): δ 3.89 (3H, s, OCH_3), 6.51 (1H, ddd, $^1J_{HC}$=160.0 Hz, $^3J_{HH}$=15.9 Hz, $^2J_{HC}$=2.7 Hz, H-8), 6.81 (1H, d, *J*=8.2 Hz, H-5), 7.06 (1H, dd, *J*=8.2, 1.9 Hz, H-6), 7.17 (1H, d, *J*=1.9 Hz, H-2), 7.59 (1H, ddd, $^3J_{HH}$=15.9 Hz, $^3J_{HC}$=6.8 Hz, $^2J_{HC}$=2.8 Hz, H-7); ^{13}C NMR (75 MHz, MeOH-d_4): δ 56.4 (OCH_3), 115.9 ($^1J_{8-9}$=73.2 Hz, $^1J_{8-7}$=69.8 Hz, C-8), 111.7 ($^3J_{2-8}$=4.4 Hz, C-2), 117.7 (C-5), 124.0 ($^3J_{6-8}$=4.9 Hz, C-6), 127.8 ($^3J_{1-9}$=6.5 Hz, C-1), 146.9 ($^1J_{7-8}$=69.8 Hz, C-7), 147.3 (C-4), 149.3 (C-3), 170.9 ($^1J_{9-8}$=73.2 Hz, C-9).

3.4.3. Preparation of [8′,9′-$^{13}C_2$]avenanthramide B. [8′,9′-$^{13}C_2$]Avenanthramide B was synthesized according to the method described in Ref. 30 with a slight modification. [8,9-$^{13}C_2$]Ferulic acid (51 mg) and 5-hydroxyanthranilic acid (73 mg) were dissolved in dry pyridine (6 ml), followed by addition of dicyclohexylcarbodiimide (224 mg). The mixture was stirred for 24 h at room temperature. After evaporation of the solvent, the residue was dissolved in MeOH (40 ml), and 5 N KOH (10 ml) was added. The mixture was kept for 24 h at room temperature in darkness. After neutralization with HOAc, MeOH was evaporated in vacuo, and the precipitated dicyclohexylurea and salts were removed by filtration. The filtrate was fractionated using an ODS column (100 mm long, 50 mm i.d.) by stepwise elution with 600 ml of each of the mixtures of MeOH–H_2O–HOAc (0:100:2, 30:70:2, 60:40:2 and 80:20:2). [8′,9′-$^{13}C_2$]Avenanthramide B was eluted in the 60% MeOH fraction. Finally, [8′,9′-$^{13}C_2$]avenanthramide B was purified by preparative HPLC [eluent, B–A (45:55); detection, 340 nm] (rt 45.2 min, yield 43 mg, 52.1%). EIMS 70 eV *m/z* (rel. int.): 331 $[M]^+$ (11), 313 $[M-H_2O]^+$ (4), 179 (100), 147 (41); ^{1}H NMR (300 MHz, MeOH-d_4): δ 3.92 (3H, s, OCH_3), 6.51 (1H, ddd, $^1J_{HC}$=157 Hz, $^3J_{HH}$=15.6 Hz, $^2J_{HC}$=3.8 Hz, H-8′), 6.82 (1H, d, *J*=8.2 Hz, H-5′), 7.03 (1H, dd, *J*=9.0, 3.0 Hz, H-4), 7.09 (1H, dd, *J*= 8.2, 1.7 Hz, H-6′), 7.21 (1H, d, *J*=1.7 Hz, H-2′), 7.52 (1H, d, *J*=3.0 Hz, H-6), 7.56 (1H, ddd, $^3J_{HH}$=15.6 Hz, $^3J_{HC}$=6.6 Hz, $^2J_{HC}$=2.5 Hz, H-7′), 8.46 (1H, d, *J*=9.0 Hz, H-3); ^{13}C NMR (75 MHz, MeOH-d_4): δ 56.4 (OCH_3), 111.5 ($^3J_{2'-8'}$=4.1 Hz, C-2′), 116.4 (C-5′), 118.1 (C-6), 119.2 (C-1), 119.6 ($^1J_{8'-9'}$=66.7 Hz, $^1J_{8'-7'}$=71.6 Hz, C-8′), 122.0 (C-4), 123.4 (C-3), 123.8 ($^3J_{6'-8'}$=5.0 Hz, C-6′), 128.0 ($^3J_{1'-9'}$=5.8 Hz, C-1′), 134.8 (C-2), 143.3 ($^1J_{7'-8'}$=71.6 Hz, C-7′), 149.3 (C-4′), 150.1 (C-3′), 154.1 (C-5), 166.6 ($^1J_{9'-8'}$=66.7 Hz, C-9′), 171.2 (C-7).

3.5. Enzymatic preparation of compound 1 and 1* labeled with ^{13}C atoms

The intercellular washing solution (IWS), which contains strong peroxidase activity, was obtained from elicited leaves (ca. 1.6 g) with 40 ml of 200 mM NaCl in KPi buffer (5 mM, pH 6.9) according to the methods described in Ref. 31. Avenanthramide B (300 mg) dissolved in 46 ml of DMSO was added to 1.4 l of McIlvaine buffer (pH 6.0), to which 1.2 ml of 30% H_2O_2, and 30 ml of IWS were added. The mixture was incubated at 30 °C for 3 h, then 30 ml of

HOAc was added. The product **1** was purified from the mixture by ODS column chromatography (210 mm long, 4.3 mm i.d.) and preparative HPLC (yield 90.6 mg, 30.3%) as described for the isolation of **1** from the elicitor solution. When horseradish peroxidase (1 μunit, Wako Pure Chemical Industries, Osaka) was added to the reaction mixture containing avenanthramide B (49 μg), the formation of **1** (15.5 μg, yield 31.7%) was detected by HPLC. A similar reaction with [8′,9′-$^{13}C_2$]avenanthramide B (30 mg) with IWS fraction of elicited oat leaves afforded **1*** (yield 8.6 mg, 28.8%).

3.5.1. 1-(2-Carboxy-4-hydroxyphenyl)-*E*-4-(4-hydroxy-3-methoxybenzylidene)-2-(4-hydroxy-3-methoxyphenyl)-5-oxopyrrolidine-3-carbamoyl-5-hydroxyanthranilate (bisavenanthramide B, 1). Yellowish solid, mp 196–198 °C. UV (MeOH) λ_{max} nm (log ε): 204 (4.61), 265 (4.31), 329 (4.45); IR (nujol) ν_{max} (cm^{-1}): 3190, 1661, 1603, 1518, 1290, 1215; ion-spray MS *m/z* (rel. int.): 679 $[M+Na]^+$ (30), 657 $[M+H]^+$ (100), 639 $[M+H-H_2O]^+$ (28), 288 (32); HRFABMS *m/z*: 657.1708, $[M+H]^+$ (calcd for $C_{34}H_{29}N_2O_{12}$: 657.1720); ^1H NMR: δ 3.73 (3H, s, CH_3O-D3), 3.76 (3H, s, CH_3O-B3), 4.28 (1H, m, H-3), 5.33 (1H, d, *J*=3.6 Hz, H-2), 6.73 (1H, d, *J*=8.1 Hz, H-B5), 6.75–6.90 (4H, overlapping signals, H-A5, A6, B6 and D5), 6.94 (1H, dd, *J*=9.0, 3.0 Hz, H-C5), 6.99 (1H, bs, H-B2), 7.04 (1H, dd, *J*=8.3, 1.7 Hz, H-D6), 7.07 (1H, d, *J*=1.7 Hz, H-D2), 7.36 (1H, d, *J*=2.7 Hz, H-A3), 7.38 (1H, d, *J*=3.0 Hz, H-C3), 7.69 (1H, d, *J*=2.2 Hz, H-1′), 8.23 (1H, d, *J*=9.0 Hz, H-C6); ^{13}C NMR (75 MHz, MeOH-d_4), see Table 1.

3.5.2. [3,4,5,6-$^{13}C_4$] 1-(2-Carboxy-4-hydroxyphenyl)-*E*-4-(4-hydroxy-3-methoxybenzylidene)-2-(4-hydroxy-3-methoxyphenyl)-5-oxopyrrolidine-3-carbamoyl-5-hydroxyanthranilate (1*). Yellowish solid; ion-spray MS *m/z* (rel. int.): 683 $[M+Na]^+$ (29), 661 $[M+H]^+$ (100), 643 $[M+H-H_2O]^+$ (37), 288 (29); ^1H NMR: δ 3.73 (3H, s), 3.76 (3H, s), 4.28 (1H, broad doublet, $^1J_{HC}$=140 Hz), 5.33 (1H, multiplet), 6.73 (1H, d, *J*=8.1 Hz), 6.75–6.90 (4H, overlapping signals), 6.94 (1H, dd, *J*=9.0, 3.0 Hz), 6.99 (1H, bs), 7.04 (1H, dd, *J*=8.3, 1.7 Hz), 7.07 (1H, d, *J*=1.7 Hz), 7.36 (1H, d, *J*=2.7 Hz), 7.38 (1H, d, *J*=3.0 Hz), 7.69 (1H, triplet-like multiplet), 8.23 (1H, d, *J*=9.0 Hz); ^{13}C NMR (75 MHz, MeOH-d_4): δ 56.3, 56.4, 57.1 ($^1J_{3-6}$=51 Hz, $^1J_{3-4}$=42 Hz, $^2J_{3-5}$=5.4 Hz), 69.2 ($^1J_{2-3}$=30 Hz, $^2J_{2-3\text{ or }6}$= 6.7 Hz), 111.8, 113.5 ($^3J_{D24}$=4.1 Hz), 116.3, 116.5, 118.1, 118.8, 120.1, 120.4, 121.6, 121.7, 123.8, 125.9 ($^1J_{4-5}$= 63 Hz, $^1J_{4-3}$=42 Hz), 126.3, 127.6 ($^2J_{D14}$=6.7 Hz), 129.5, 131.1, 132.8, 133.6, 138.2 ($^1J_{1'-4}$=75 Hz), 147.9, 149.1, 149.4, 149.7, 154.6, 157.9, 168.4, 170.1, 170.7 (overlapping signals, C-5 and 6).

3.6. Preparation of compound 2 and 2*

Compound **1** prepared by the enzyme reaction (90.6 mg) was refluxed with 1 N HCl (180 ml) at 120 °C for 48 h under argon gas. The reaction mixture was neutralized with 5 N NaOH, and loaded onto an ODS column (140 mm long, 30 mm i.d.) equilibrated with H_2O. The column was washed with 300 ml of H_2O, and eluted with 300 ml of MeOH. The MeOH fraction was concentrated and subjected to preparative HPLC [eluent, B–A (30:70); detection, 280 nm] to give **2** (rt 48.8 min, yield 33.5 mg, 46.6%). The neutralized reaction mixture was also analyzed by HPLC equipped with a Shimadzu M10Avp photodiode array detector [column; AQUA 3u C18 125A, 150 mm long, 4.6 mm i.d.; eluent, H_2O–TFA (100:0.1); flow rate, 0.8 ml min^{-1}; column temperature, 40 °C] to confirm the release of 5-hydroxyanthranilic acid (rt 4.9 min). The peak corresponding to 5-hydroxyanthranilic acid showed the same UV spectrum as the authentic compound. The same procedure with **1*** (8.60 mg) gave **2*** (yield 3.01 mg, 50.2%).

3.6.1. 1-(2-Carboxy-4-hydroxyphenyl)-*E*-4-(4-hydroxy-3-methoxybenzylidene)-2-(4-hydroxy-3-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (2). Yellow solid, mp 176–178 °C. UV (MeOH) λ_{max} nm (log ε): 203 (4.80), 233 sh (4.33), 300 sh (4.22), 330 (4.37); IR (nujol) ν_{max} (cm^{-1}): 3374, 3188, 1708, 1666, 1632, 1603, 1518; ion-spray MS *m/z* (rel. int.): 522 $[M+H]^+$ (100), 504 $[M+H-H_2O]^+$ (9); HRFABMS *m/z*: 522.1396, $[M+H]^+$ (calcd for $C_{27}H_{24}NO_{10}$: 522.1400); ^1H NMR (300 MHz, MeOH-d_4): δ 3.73 (3H, s, CH_3O-B3), 3.86 (3H, s, CH_3O-D3), 4.21 (1H, m, H-3), 5.33 (1H, d, *J*=3.6 Hz, H-2), 6.71 (1H, d, *J*=8.1 Hz, H-B5), 6.77 (1H, dd, *J*=8.1, 1.8 Hz, H-B6), 6.82 (1H, dd, *J*=8.7, 2.8 Hz, H-A5), 6.83 (1H, d, *J*=8.2 Hz, H-D5), 6.91 (1H, d, *J*=8.7 Hz, H-A6), 6.99 (1H, d, *J*=1.8 Hz, H-B2), 7.04 (1H, dd, *J*=8.2, 1.8 Hz, H-D6), 7.11 (1H, d, *J*=1.8 Hz, H-D2), 7.33 (1H, d, *J*=2.8 Hz, H-A3), 7.52 (1H, d, *J*=2.2 Hz, H-1′); ^{13}C NMR (75 MHz, MeOH-d_4), see Table 1.

3.6.2. [3,4,5,6-$^{13}C_4$] 1-(2-Carboxy-4-hydroxyphenyl)-*E*-4-(4-hydroxy-3-methoxybenzylidene)-2-(4-hydroxy-3-methoxyphenyl)-5-oxopyrrolidine-3-carboxylic acid (2*). Yellow solid; ion-spray MS *m/z* (rel. int.): 526 $[M+H]^+$ (100), 508 $[M+H-H_2O]^+$ (11); ^1H NMR (300 MHz, MeOH-d_4): δ 3.73 (3H, s), 3.86 (3H, s), 4.21 (1H, broad doublet, $^1J_{HC}$=136 Hz), 5.33 (1H, multiplet), 6.71 (1H, d, *J*=8.1 Hz), 6.77 (1H, dd, *J*=8.1, 1.8 Hz), 6.82 (1H, dd, *J*=8.7, 2.8 Hz), 6.83 (1H, d, *J*=8.2 Hz), 6.91 (1H, d, *J*=8.7 Hz), 6.99 (1H, d, *J*=1.8 Hz), 7.04 (1H, dd, *J*=8.2, 1.8 Hz), 7.11 (1H, *d*, *J*=1.8 Hz), 7.33 (1H, *J*=2.8 Hz), 7.52 (1H, triplet-like multiplet); ^{13}C NMR (75 MHz, MeOH-d_4): δ 53.7 ($^1J_{3-6}$=57.9 Hz, $^1J_{3-4}$=43.6 Hz), 56.3, 68.5, 111.6, 113.6, 116.1, 116.4, 118.6, 120.0, 121.7, 126.0, 126.8 ($^1J_{4-5}$=64.3 Hz, $^1J_{4-3}$=43.6 Hz), 127.7, 129.2, 130.2, 131.5, 132.4, 136.4, 147.9, 149.0, 149.3, 149.5, 157.7, 168.8, 170.8 ($^1J_{5-4}$=64.3 Hz), 174.2 ($^1J_{6-3}$=57.9 Hz).

3.7. Preparation of compound 3

A solution of (trimethylsilyl)diazomethane (2.0 M in diethylether, 2 ml) was added to a MeOH solution (6 ml) of **2** (5.7 mg). The reaction mixture in a sealed flask under nitrogen gas was stirred for 4 h at ambient temperature. Excess (trimethylsilyl)diazomethane was decomposed by addition of HOAc (ca. 2 ml). After standing for 30 min, the solvent was evaporated in vacuo and subjected to preparative HPLC [eluent, B–A (53:47); detection, 280 nm] to give **3** (rt 59.8 min; yield 5.1 mg, 79.3%).

3.7.1. *E*-4-(3,4-Dimethoxybenzylidene)-2-(3,4-dimethoxyphenyl)-1-(4-methoxy-2-methoxycarbonylphenyl)-5-oxopyrrolidine-3-carboxylic acid methyl ester

(3). Yellowish white solid, mp 190–192 °C. UV (MeOH) λ_{max}nm (log ε): 204 (4.72), 234 sh (4.33), 306 sh (4.20), 331 (4.32); IR (nujol) ν_{max} (cm^{-1}): 1728, 1692, 1645, 1597, 1516, 1504, 1265, 1231; ion-spray MS *m/z* (rel. int.): 592 $[M+H]^+$ (100), 560 $[M+H-CH_3OH]^+$ (70), 528 (8), 500 (14), 411 (13), 383 (17). EIMS 70 eV *m/z* (rel. int.): 591 $[M]^+$ (62), 532 (60), 500 (38), 453 (23), 329 (24), 314 (40), 262 (100); HREIMS *m/z*: 591.2112, $[M]^+$ (calcd for $C_{32}H_{33}NO_{10}$: 591.2104); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69 (3H, s, CH_3O-6), 3.785 (3H, s, CH_3O-A4), 3.793 (3H, s, CH_3O-B3), 3.84 (3H, s, CH_3O-B4), 3.87 (3H, s, CH_3O-D3), 3.88 (3H, s, CH_3O-A7), 3.91 (3H, s, CH_3O-D4), 4.21 (1H, m, H-3), 5.23 (1H, d, *J*=3.7 Hz, H-2), 6.76 (1H, d, *J*=8.2 Hz, H-B5), 6.84 (1H, dd, *J*=8.2, 1.8 Hz, H-B6), 6.85–6.88 (2H, overlapping signals, H-A5 and A6), 6.87 (1H, d, *J*=8.4 Hz, H-D5), 6.97 (1H, d, *J*=1.8 Hz, H-B2), 7.00 (1H, d, *J*=1.8 Hz, H-D2), 7.08 (1H, dd, *J*=8.4, 1.8 Hz, H-D6), 7.39 (1H, triplet-like dd, *J*=1.5 Hz, H-A3), 7.67 (1H, d, *J*=2.2 Hz, H-1′); ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1.

3.8. Optical resolution of 1

Compound **1** prepared by the enzyme reaction was subjected to optical resolution by HPLC with a chiral column [column, CHIRALCEL OD-RH, 150 mm long, 4.6 mm i.d.; eluent, MeCN200 mM KH_2PO_4 aq. (13:87); flow rate, 0.8 ml min^{-1}; column temperature, 40 °C; detection, 330 nm]. Compound **1** eluted as two peaks (rt 13.6 min and 15.8 min) with almost the same peak area. The collection of the fractions corresponding to the peaks resulted in the separation of enantiomers. The fractions were diluted 3-fold with H_2O, and applied to an ODS column equilibrated with H_2O to remove KH_2PO_4. The column was eluted with MeOH, and the eluate was concentrated in vacuo. The collection of the enantiomer eluted first gave (+)-**1** (1.55 mg, 100% e.e.), $[\alpha]_D$=+92.4° (*c*=0.155, MeOH, 22 °C). The collection of the enantiomer eluted second gave (−)-**1** (2.12 mg, 75.7% e.e.), $[\alpha]_D$=−82.8° (*c*=0.212, MeOH, 22 °C), with an absolute value of $[\alpha]_D$=−86.9° calculated for optically pure (−)-**1**. Compound **1** purified from the elicitor solution was also separated into two peaks (rt 13.6 and 15.8 min) with the same peak area on chiral HPLC under the conditions described above.

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Imidomethylation of *C*-nucleophiles using O-phthalimidomethyl trichloroacetimidate and catalytic amounts of TMSOTf

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Abstract—The *O*-phthalimidomethyl trichloroacetimidate (**1**), as a latent aminomethylating agent, exhibits high electrophilicity towards a variety of *C*-nucleophiles in the presence of catalytic amounts of TMSOTf and mild reaction conditions. The nucleophiles include aromatics, alkenes and active methylene compounds **2**–**11** whereby a phthalimidomethyl group could be introduced to give compounds **12**–**22**. Removal of the phthaloyl group gave the respective amines, β-amino ketones, and β-amino acids. The *O*-(trichloroacetamido)methyl trichloroacetimidate (**35**) was also found to be a good amidomethylating agent.

1. Introduction

The development of methodologies for *C*–*C* bond formation,[1] particularly those involving introduction of one carbon atom bearing a functional group into the skeleton of organic molecules, is of high interest. When such a functional group is an alkyl- or an acyl-amino group linked via the nitrogen to a methylene group carrying a leaving group such as halogen, OR or NR_2, the process is called amino or amidomethylation.[1–5] Commonly, these reagents are electrophiles and for linkage to the other reactant a nucleophilic center is required. Much work has been devoted to the aminomethylation of activated carbon atoms by reaction with formaldehyde and amines.[1] Organometallic derivatives derived from alkenes and aromatic compounds can be aminomethylated.[1–9] Such aminomethylation processes are usually providing products with amino alkyl groups. On the other hand, amidomethylations provide amides that could be hydrolyzed to the corresponding amines. The use of formaldehyde and amides for the amidomethylation of activated carbons was not successful.[1] However, such reactions were successful when using *N*-hydroxy-methyl amides,[10] a method which was then further developed.[11–15] The hydroxy group in the latter reagent has been replaced by a leaving group such as esters,[15] halogens[13] and substituted amines.[12,16,17] The respective cyclic imides of dicarboxylic or sulfocarboxylic acids were also used in corresponding imidomethylations.[12,18–21] The reaction required the use of strong acid and heating for long periods of time which could reach 24 h.[4] Owing to the importance of amino and amidomethylation in organic synthesis and compounds possessing such a group, it became of interest to develop a method which requires mild reaction conditions and only catalytic amounts of the promoters. Towards this end, we have investigated the reaction of the recently developed reagent, *O*-phthalimidomethyl (Pim) trichloroacetimidate (**1**)[22] with different types of *C*-nucleophiles; this reagent has been also successfully employed for *O*-protection via imidomethylation of *O*-nucleophiles. Now, a methodology has been developed for introducing the phthalimidomethyl group on carbon nucleophiles to form a *C*–*C* bond using *O*-phthalimidomethyl trichloroacetimidate (**1**),[11] as imidomethylating agent with the phthalimido group acting as an amino protecting group (Scheme 1). The reaction proceeded smoothly in the presence of catalytic amounts of TMSOTf under mild conditions and at room temperature. Moreover, a practical approach for the synthesis of β-amino ketones and β-amino esters will be reported.

2. Results and discussion

Reaction of the trichloroacetimidate **1** with the silylated *C*-nucleophile allyl trimethylsilane (**2**) in the presence of catalytic amounts of TMSOTf at room temperature gave **12** in 93% yield (Scheme 1, Table 1); compound **12** was previously prepared by the nucleophilic displacement of the tosyloxy group in 1-tosyloxy-3-butene with potassium phthalimide.[23] Similarly, trichloroacetimidate **1** was reacted with 1,3-dimethoxy-benzene (**3**) and 1,2,3-trimethoxy-benzene (**4**) to give **13** and **14** in 78 and 87% yield,

Keywords: *O*-Phthalimidomethyl trichloroacetimidate; Imidomethylation; Amidomethylation; Amino ketones; Amino acids.
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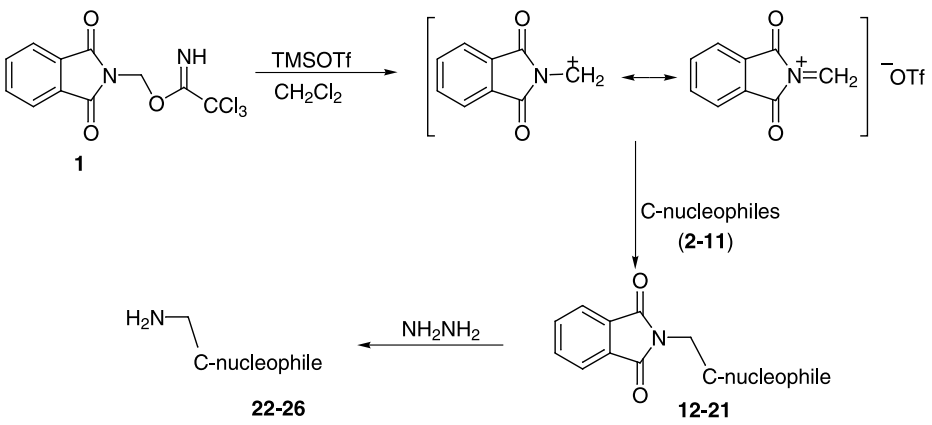


Scheme 1.

respectively. **1** reacted also with benzene (**5**) to give **15** in 86% yield which is available by Mitsunobu reaction of benzyl alcohol with phthalimide[24–27] and by reaction of benzylamine[29] or benzylazide[28,29] with phthalic anhydride. Compounds **13**–**15** were readily identified by ^{1}H NMR spectra which showed a singlet at δ 4.82–4.84 characteristic for the introduced methylene group, in addition to the signals of the aromatic protons which confirm the position of the imidomethyl group on the ring.

The trichloroacetimidate **1** was found to be also a suitable precursor for the synthesis of (*Z*/*E*)-1-phenyl-3-phthalimido-2-propene (**16**) in 85% yield upon reaction with phenylethylene (styrene) (**6**); the ratio of *Z*/*E* in **16** is 1:1 as determined from its ^{1}H NMR spectrum. Compound **16** was already prepared from (3-chloro-allyl)-benzene and the potassium salt of phthalimide.[30]

The trichloroacetimidate **1** has been also found to be an excellent reagent for the imidomethylation of the α-position of ketones and acids as shown in Table 2. Thus, compound **17**[31] was readily prepared by reaction of trichloroacetimidate **1** with 1-trimethylsiloxy-cyclohexene (**7**) as *C*-nucleophile. The reaction of trichloroacetimidate **1** with

Table 1. Phthalimidomethylation of *C*-nucleophiles **2**–**6** by **1**

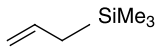
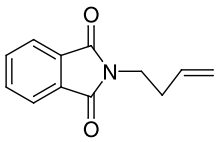
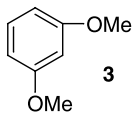
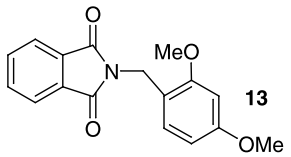
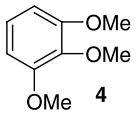
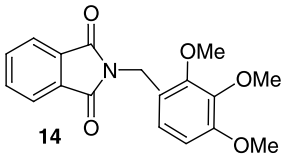
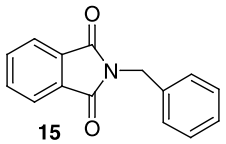
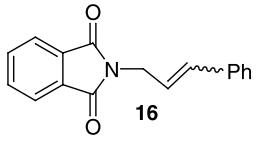
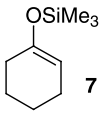
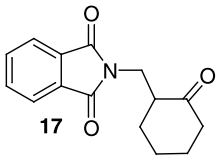
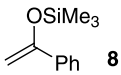
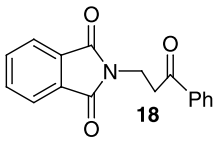
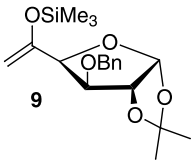
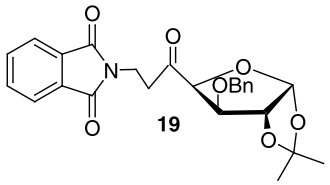
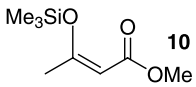
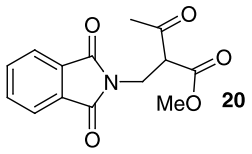
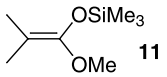
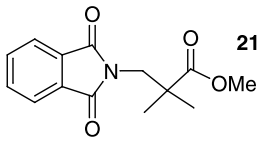
Entry	*C*-Nucleophile	Product	Time (min)	Yield (%)
1	 **2**	 **12**	60	93
2	 **3**	 **13**	60	78
3	 **4**	 **14**	45	87
4	 **5**	 **15**	180	86
5	 **6**	 **16**	60	85

Table 2. Phthalimidomethylation of *C*-nucleophiles **7**–**11** by **1**

Entry	*C*-Nucleophile	Product	Time (min)	Yield (%)
6	 **7**	 **17**	30	89
7	 **8**	 **18**	20	83
8	 **9**	 **19**	10	87
9	 **10**	 **20**	45	75
10	 **11**	 **21**	60	82

1-phenyl-1-trimethylsiloxy-ethylene (**8**) in the presence of TMSOTf gave **18** in 83% yield. The synthesis of **18** was already reported[32] by using Michael-type addition of phthalimide to phenyl vinyl ketone. The reaction of **1** on the 6-position of glucose derived enol ether **9**[33] gave 3-*O*-benzyl-6,7-dideoxy-1:2-*O*-isopropylidene-7-(phthalimido)-α-D-xylo-heptofuranos-5-ulose (**19**) in 87% yield. The generated *C*–*C* linkage in the product was confirmed by the presence of two signals at δ 3.04 and 3.96 for the CH_2–CH_2 group which was confirmed by the ^{13}C NMR spectrum displaying signals at δ 32.4 and 39.0.

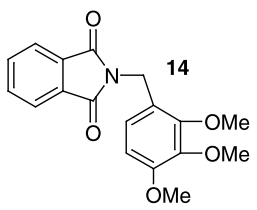
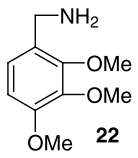
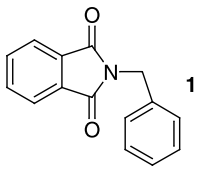
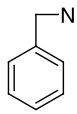
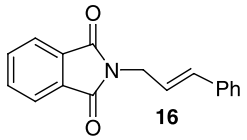
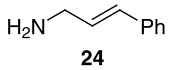
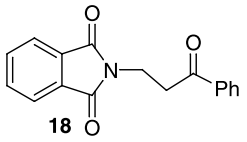
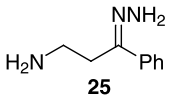
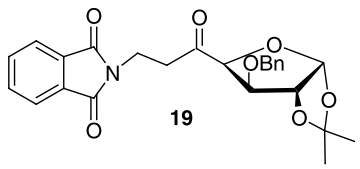
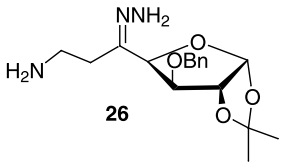
β-Amino acids and their derivatives are an important class of compounds. They are present in many biologically active compounds and in the free form they show interesting pharmacological effects.[34] They are also precursors of the β-lactam moiety which is present in some antibiotics. Again, the trichloroacetimidate **1** was reacted with silylated reagents such as 3-trimethylsiloxy-2-butenic acid methyl ester (**10**) and 1-methoxy-2-methyl-1-trimethylsiloxy-propene (**11**) in the presence of TMSOTf to give **20** and **21** in 75 and 82% yield, respectively.[37] Compound **20** was identified by ^1H NMR spectroscopy which showed the newly introduced imidomethylene group at δ 4.13 and signals of the benzene ring at δ 7.61–7.88.

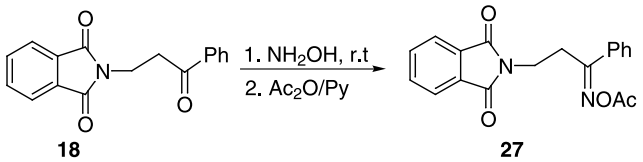
After performing successfully the imidomethylation on the selected *C*-nucleophiles, it became interesting to achieve a deprotection of the amino group. Hydrazine hydrate in refluxing methanol has been selected to remove the phthalimido group, which worked successfully to give the respective amines **22**,[36] **23** and **24**[37] from **14**, **15** and **16**, respectively (Table 3). In case of the β-aminoketones **18** and **19**, a concomitant reaction of the carbonyl groups with hydrazine, in addition to the deprotection, had taken place to give the hydrazones **25** and **26**, respectively.

Attempted deprotection of the phthalimido group by heating with hydroxylamine even for long time and with more reagent did not cause its hydroxylaminolysis and the product from the reaction was found to be the corresponding oxime whose acetylation gave **27**. The failure of the cleavage is due to the lower nucleophilicity of the hydroxylamine compared to hydrazine (Scheme 2).

The successful imidomethylation via the trichloroacetimidate **1** as shown above, and on the other hand the failure of reacting formaldehyde and amides with activated carbons, attracted our attention to explore the reactivity of the *N*-methylol amides as amidomethylating agents via their trichloroacetimidates. Thus *N*-methyl-olben-zamide (**28**)[38] and *N*-methylmethylol benzamide (**29**)[39] were reacted with trichloroacetonitrile in dichloromethane as solvent in the presence of DBU or NaH for activating the hydroxyl group towards the reaction with the nitrile group (Scheme 3).[40–42] The reaction was carried out at different temperatures (−50 °C, 0 °C, room temperature). However, in no case the expected trichloroacetimidates **30** and **31**, respectively,

Table 3. Hydrazinolysis of phthalimido derivatives **14**–**19**

Entry	Phthaloyl derivatives	Product	Yield (%)
1	 **14**	 **22**	84
2	 **15**	 **23**	92
3	 **16**	 **24**	76
4	 **18**	 **25**	78
5	 **19**	 **26**	66



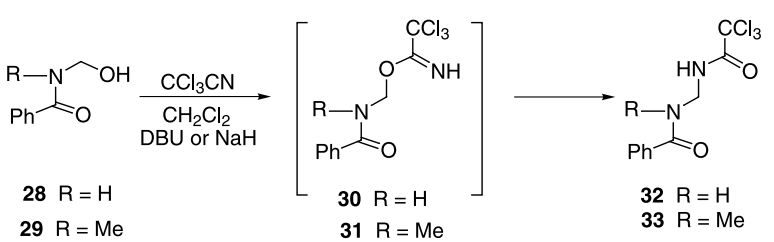
18 **27**

Scheme 2.

could be obtained; the isolated products were found to have, in accordance with the Chapman rearrangement, the structure of the trichloroacetamides **32** and **33**. Similar rearrangements can be also observed upon activation of *O*-glycosyl trichloroacetimidates in the presence of poor glycosyl acceptors.[40–42] The structures of **32** and **33** were established through their ^{1}H NMR spectra which reveal the presence of a methylene moiety between two NH groups for **32** which appeared as a doublet of doublet at δ 4.98, whereas that of **33** appeared as a doublet at δ 5.00.

When the phenyl group in the above amides was changed to the electron withdrawing trichloromethyl group as in *N*-hydroxymethyl trichloroacetamide (**34**),[43] and reacting the latter with trichloroacetonitrile in the presence of NaH as base at room temperature, as expected the trichloroacetimidate **35** was formed without rearrangement and in good yield (Scheme 4). The structure of **35** was confirmed from its ^{1}H NMR spectrum which showed a doublet at δ 4.93 for the CH_2 group in addition to a signal at δ 3.95 for the NH group, whereas the other NH group appeared at δ 7.81.

The trichloroacetimidate **35** reacted readily with styrene (**6**)

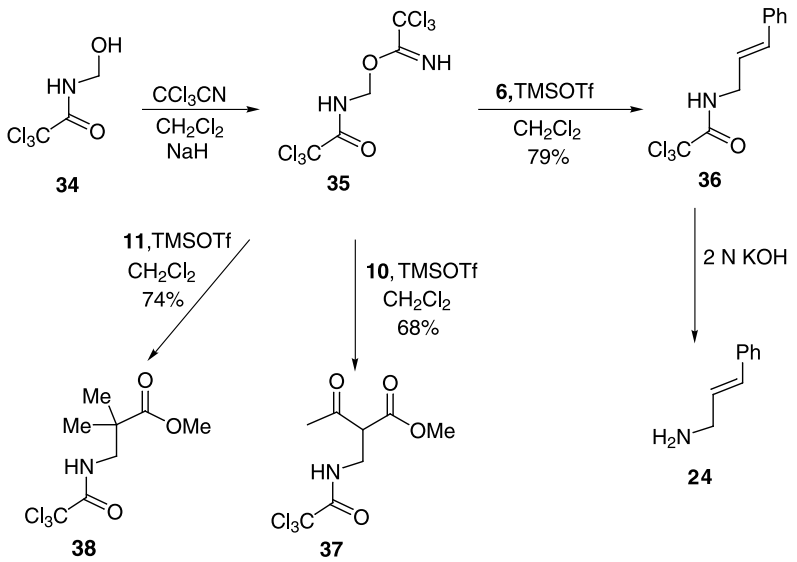


28 R = H
29 R = Me

30 R = H
31 R = Me

32 R = H
33 R = Me

Scheme 3.



Scheme 4.

to give amidomethylation product **36**[44] which can be hydrolyzed to the amine **24** with 1 N KOH. Amidomethylating agents, having different substituents, were reported to react with styrene, however in lower yields and accompanied by cyclic products.[45] **35** reacted also with the *O*-silylated nucleophiles 3-trimethylsiloxy-2-butenoic acid methyl ester (**10**) and 1-methoxy-2-methyl-1-trimethylsiloxy-propene (**11**) under the same conditions to afford **37** and **38**, respectively, in good yield.

In conclusion, a general method has been developed for introducing the *N*-phthalimidomethyl group (Pim) on a variety of carbon nucleophiles. The Pim trichloroacetimidate **1** can be considered as a reagent of choice for forming *C*–*C* bonds with nucleophiles under mild conditions in the presence of only catalytic amounts of TMSOTf. Trichloroacetimidate **1** is characterized by a high electrophilic reactivity. The high reactivity is due to the electron withdrawing nature of the carbonyl groups which increased its electrophilicity.[46] Reagent **1** can be stored without decomposition and the respective derivatives can be easily isolated and identified. On the other hand, deprotection of the phthalimido group to give the aminomethylated analogues can be readily achieved. Thus, novel approaches for β-amino ketones and β-amino acids are available. Preliminary results with *O*-(trichloroacetamidomethyl)trichloroacetimidate **35** proved also its successful application as amidoalkylating agent.

3. Experimental

3.1. General methods

Melting points are uncorrected. Thin-layer chromatography (TLC) was performed on plastic plates Silica Gel 60 F_{254}. The detection was achieved by treatment with a solution of 20 g ammonium molybdate and 0.4 g cerium (IV) sulfate in 400 mL of 10% H_2SO_4 or with 15% H_2SO_4 in methanol and heating at 150 °C. Flash chromatography was carried out on silica gel (Baker, 30–60 μm). Optical rotations were determined at 20 °C with a Perkin–Elmer 241 MC polarimeter (1 dm cell). NMR spectra were recorded with Bruker AC 250 and 600 DRX instruments, using tetramethylsilane as an internal standard. The assignment of ^{13}C NMR spectra were based on carbon-proton shift-correlation heteronuclear multiple quantum coherence (HMQC). Mass spectra were recorded with MALDI-Kompakt (Kratos) and FAB with Finningen Mat 312/AMD. Microanalyses were performed in the Microanalysis Unit at the Department of Chemistry, University of Konstanz.

3.2. General procedure for the reaction of *O*-phthalimidomethyl trichloroacetimidate (1) with *C*-nucleophiles

A stirred solution of **1** (0.45 g, 1.4 mmol) and *C*-nucleophiles as acceptor (1.4 mmol) in dry dichloromethane (40 mL) under nitrogen was treated with TMSOTf (13 μL, 0.06 mmol) at room temperature. After completion of the reaction (TLC), the mixture was neutralized with solid sodium bicarbonate, filtered and concentrated in vacuo. The residue was purified by flash chromatography.

3.2.1. *N*-But-3-enyl-phthalimide (12). White powder (0.26 g, 93%); R_f 0.64 (petroleum ether/ethyl acetate, 5:1). Mp 48 °C, lit.[24] 49–50 °C. The analytical data are identical with the published values.

3.2.2. *N*-(2,4-Dimethoxybenzyl)phthalimide (13). White powder (0.32 g, 78%); R_f 0.43 (petroleum ether/ethyl acetate, 5:1). Mp 91 °C. ^1H NMR (250 MHz, $CDCl_3$): δ 3.76 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.82 (s, 2H, CH_2), 6.38–7.13 (m, 3H, Ar-H), 7.67–7.87 (m, 4H, Ar-H); ^{13}C NMR (62.8 MHz, $CDCl_3$): δ 36.5 (CH_2), 55.2, 55.4 ($2OCH_3$), 98.5, 103.8, 116.6, 122.8, 123.1, 129.7, 132.1, 133.5, 133.8 (C-Ar), 160.5, 168.1 (2CO); MS: *m/z* 297.0. Anal. calcd for $C_{17}H_{15}NO_4$ (297.3): C, 68.68; H, 5.08; N, 4.71. Found: C, 68.58; H, 5.16; N, 4.78.

3.2.3. *N*-(2,3,4-Trimethoxybenzyl)phthalimide (14). White powder (0.40 g, 87%); R_f 0.48 (petroleum ether/

ethyl acetate, 5:1). Mp 106 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.81, 3.84, 3.95 (3s, 9H, $3OCH_3$), 4.84 (s, 2H, NCH_2), 6.58 (d, J=8.6 Hz, 1H, Ar-H), 6.97 (d, J=8.6 Hz, 1H, Ar-H), 7.69–7.88 (m, 4H, Ar-H); MS: m/z 327.0. Anal. calcd for $C_{18}H_{17}NO_5 \cdot 0.25H_2O$ (331.8): C, 65.15; H, 5.23; N, 4.22. Found: C, 65.27; H, 5.13; N, 4.27.

3.2.4. *N*-Benzylphthalimide (15). White powder (0.29 g, 86%); R_f 0.45 (petroleum ether/ethyl acetate, 5:1). Mp 118 °C, lit.[28] 118 °C. The analytical data are identical with the published values.

3.2.5. *N*-(*Z*/*E*)-Cinnamylphthalimide (16). White powder (0.31 g, 85%); R_f 0.67 (petroleum ether/ethyl acetate, 5:1). Mp 153 °C, lit.[30] 156–158 °C. The analytical data are identical with the published values.

3.2.6. *N*-(2-Oxo-cyclohexylmethyl)phthalimide (17). White powder (0.32 g, 89%); R_f 0.57 (petroleum ether/ethyl acetate, 5:1). Mp 133 °C, lit.[31] 134 °C.

3.2.7. *N*-(3-Oxo-3-phenylpropyl)phthalimide (18). White powder (0.32 g, 83%); R_f 0.52 (petroleum ether/ethyl acetate, 5:1). Mp 128 °C, lit.[32] 130 °C. The analytical data are identical with the published values.

3.2.8. 3-*O*-Benzyl-6,7-dideoxy-1:2-*O*-isopropylidene-7-(phthalimido)-α-D-xylo-heptofuranos-5-ulose (19). Colorless oil (0.55 g, 87%); R_f 0.72 (petroleum ether/ethyl acetate, 5:1); $[\alpha]_D$=−18.5 (c=0.5, CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.29, 1.44 (2s, 6H, $2CH_3$), 3.04 (m, 2H, CH_2), 3.96 (m, 2H, CH_2), 4.24 (d, J=3.5 Hz, 1H, 4-H), 4.46 (d, J_{gem}=11.9 Hz, 1H, CHPh), 4.53 (d, J_{gem}=11.9 Hz, 1H, CHPh), 4.55 (d, J=3.4 Hz, 1H, 2-H), 4.64 (d, J=3.5 Hz, 1H, 3-H), 6.01 (d, J=3.4 Hz, 1H, 1-H), 7.20–7.33 (m, 5H, Ar-H), 7.67–7.80 (m, 4H, Ar-H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ 26.3, 26.9 ($2CH_3$), 32.4, 39.0, 72.4 ($3CH_2$), 81.7 (2-C), 83.5 (4-C), 85.2 (3-C), 105.9 (1-C), 112.4, 123.1, 123.8, 127.6, 128.0, 128.5, 132.1, 133.8, 134.5, 136.7 (C-Ar), 167.9 (CO), 206.3 (NCO); MALDI, positive mode, Matrix: DHB): m/z=473.9 $(M+Na)^+$, 490.0 $(M+K)^+$. Anal. calcd for $C_{25}H_{25}NO_7 \cdot H_2O$ (469.5): C, 63.90; H, 5.75; N, 2.98. Found: C, 63.84; H, 5.66; N, 3.03.

3.2.9. Methyl 3-oxo-2-(phthalimidomethyl)butanoate (20). Colorless oil (0.29 g, 75%); R_f 0.48 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.20 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 3.95 (m, 1H, CH), 4.13 (m, 2H, CH_2), 7.61–7.88 (m, 4H, Ar-H); MS: m/z=275.0. Anal. calcd for $C_{14}H_{13}NO_5$ (275.3): C, 61.09; H, 4.76; N, 5.09. Found: C, 60.81; H, 4.68; N, 5.68.

3.2.10. Methyl 2,2-dimethyl-3-(phthalimido)propionate (21). White powder (0.30 g, 82%); R_f 0.53 (petroleum ether/ethyl acetate, 5:1). Mp 92 °C, lit.[35] 92–94 °C. The analytical data are identical with the published values.

3.3. General procedure for the removal of the phthaloyl group

The phthalimide derivative (0.50 mmol) was dissolved in methanol (30 mL) and hydrazine hydrate (2 mL) and then heated under reflux for 1 h. The solvent was evaporated in vacuo and the residue dissolved in dichloromethane (50 mL). The solution was extracted with 1 N NaOH (5×50 mL) and the organic layer was dried with magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol).

3.3.1. 2,3,4-Trimethoxybenzylamine (22). Yellow oil (0.08 g, 84%). The analytical data are identical with the published values.[36]

3.3.2. Benzylamine (23). Yellow oil (0.05 g, 92%). The analytical data are identical with an authentic sample.

3.3.3. 3-Phenyl-allylamine (24). Yellow oil (0.05 g, 76%). The analytical data are identical with the published values.[37]

3.3.4. 3-Amino-1-phenyl propan-1-one hydrazone (25). Yellow oil (0.05 g, 78%); R_f 0.34 (chloroform/methanol 2:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.81 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 3.51–4.20 (brs, 4H, $2NH_2$), 7.18–7.68 (m, 5H, Ar-H); MS: m/z=163.0.

3.3.5. 7-Amino-3-O-benzyl-6,7-dideoxy-1:2-*O*-isopropylidene-α-D-xylo-heptofuranos-5-ulose hydrazone (26). Colorless oil (0.44 g, 66%); R_f=0.41 (chloroform/methanol 2:1); $[\alpha]_D$=−4.6 (c=0.5, CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.27, 1.44 (2s, 6H, $2CH_3$), 2.45 (m, 2H, CH_2), 2.85 (m, 2H, CH_2), 4.01 (d, J=3.5 Hz, 1H, 4-H), 4.42 (d, J_{gem}=11.8 Hz, 1H, C*H*Ph), 4.45 (d, J_{gem}=11.8 Hz, 1H, CHPh), 4.55 (d, J=3.5 Hz, 1H, 2-H), 4.70 (d, J=3.5 Hz, 1H, 3-H), 5.11 (brs, 2H, NH_2), 5.95 (d, J=3.5 Hz, 1H, 1-H), 7.13–7.31 (m, 5H, Ar-H). Anal. calcd for $C_{17}H_{25}N_3O_4 \cdot 0.25H_2O$ (340.4): C, 60.07; H, 7.41; N, 12.36. Found: C, 60.14; H, 7.49; N, 11.74.

3.3.6. 1-Phenyl-3-(phthalimido)-propan-1-one *O*-acetyl-oxime (27). Compound **17** (0.2, 0.7 mmol) was dissolved in dry methanol (20 mL) and hydroxylamine hydrochloride (0.15 g) was added. A solution of 10% NaOMe in methanol was added dropwise until pH=10 and then stirred for 1 h. The mixture was filtered and evaporated in vacuo. The residue was dissolved in pyridine (5 mL), treated with acetic anhydride (2.5 mL) and the mixture was stirred at room temperature for 12 h. The solvent was evaporated in vacuo and then co-evaporated with toluene and the residue was purified by flash chromatography (dichloromethane/methanol 10:1) to afford **27** (0.19 g, 79%) as colorless oil; R_f 0.71 (chloroform/methanol 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3CO), 3.24 (t, J=7.2 Hz, 2H, CH_2), 3.96 (t, J=7.2 Hz, NCH_2), 7.24–7.38 (m, 5H, Ar-H), 7.67–7.82 (m, 4H, Ar-H); MALDI, positive mode, Matrix: DHB): m/z=358.4 $(M+Na)^+$, 375.1 $(M+K)^+$. Anal. calcd for $C_{19}H_{16}N_2O_4 \cdot 0.5H_2O$ (345.34): C, 66.08; H, 4.95; N, 8.11. Found: C, 66.14; H, 4.90; N, 7.91.

3.3.7. *N*-(Trichloroacetamidomethyl)benzamide (32). A stirred solution of *N*-hydroxymethylol benzamide (**28**) (0.76 g, 5.0 mmol) in dry dichloromethane (20 mL) and trichloroacetonitrile (5 mL, 50 mmol) was treated with DBU (71 μL) at room temperature and then left for 12 h. The solvent was evaporated and the product was purified by column chromatography (2% triethylamine in toluene) to give **32** as a white powder (0.80 g, 54%); R_f 0.62 (2%

triethylamine in toluene). Mp 115 °C. NaH can be used instead of DBU to give (1.3 g, 86.5%). ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.98 (dd, J=7.0 Hz, 2H, CH_2), 7.41–7.81 (m, 6H, NH, Ar-H), 8.12 (br, 1H, NH). ^{1}H NMR (250 MHz, DMSO-d_6): δ 5.00 (s, 2H, CH_2), 7.68–8.21 (m, 5H, Ar-H), 9.40 (br, 1H, NH), 9.81 (br, 1H, NH); MS: m/z=295.5. Anal. calcd for $C_{10}H_9Cl_3N_2O_2$ (295.5): C, 40.64; H, 3.07; N, 9.48. Found: C, 40.62; H, 3.10; N, 9.35.

3.3.8. *N*-(Trichloroacetamidomethyl)-*N*-methyl-benzamide (33). A stirred solution of *N*-hydroxymethyl *N*-methyl benzamide **29** (0.83 g, 5.0 mmol) in dry dichloromethane (20 mL) and trichloroacetonitrile (5 mL, 50 mmol) was treated with NaH (0.12 g, 5 mmol) at room temperature and then left for 8 h. The reaction mixture was processed as above. The crude residue was purified by column chromatography (2% triethylamine in toluene) to give **33** as a white powder (0.1 g, 73%); R_f 0.71 (2% triethylamine in toluene). Mp 95 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.11 (s, 3H, CH_3), 4.98 (d, J=5.8 Hz, 2H, CH_2), 7.42 (m, 5H, Ar-H), 8.01 (br, 1H, NH). MALDI, positive mode, Matrix: DHB): m/z=332.0 $(M+Na)^+$. Anal. calcd for $C_{11}H_{11}Cl_3N_2O_2$ (309.6): C, 42.68; H, 3.58; N, 9.05. Found: C, 42.69; H, 3.59; N, 9.20.

3.3.9. *O*-(Trichloroacetamidomethyl) trichloroacetimidate (35). A stirred solution of *N*-hydroxymethyl-trichloroacetamide (**34**) (0.96 g, 5.0 mmol) in dry dichloromethane (20 mL) and trichloroacetonitrile (5 mL, 50 mmol) was treated with NaH (0.12 g, 5 mmol) at room temperature and then left for 8 h. The reaction was processed as above. The crude residue was purified by column chromatography (2% triethylamine in toluene) to give **35** as an oil (1.2 g, 71.5%); R_f 0.69 (2% triethylamine in toluene). ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.95 (br, 1H, NH), 4.93 (d, J=6.4 Hz, 2H, CH_2), 7.81 (brs, 1H, NH). ($C_5H_4Cl_6N_2O_2$) 337.0; m/z=337.0.

3.4. General procedure for the reaction of trichloroacetimidate 35 with *C*-nucleophiles

A solution of **35** (0.47 g, 1.4 mmol) and acceptor (1.4 mmol) in dry dichloromethane (40 mL) was stirred under nitrogen at room temperature and then TMSOTf (13 μL, 0.06 mmol) was added. After 1–3 h, the reaction mixture was neutralized with solid sodium bicarbonate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate).

3.4.1. *N*-(3-Phenyl-allyl)-trichloroacetamide (36). Yellow oil (0.21g, 79%). The analytical data are identical with the published values.[44]

3.4.2. Methyl 3-oxo-2-(trichloroacetamidomethyl)-butanoate (37). Colorless oil (0.27 g, 68%); R_f 0.46 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.35 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.92 (m, 3H, CH, NCH_2), 7.51 (brs, 1H, NH). Anal. calcd for $C_8H_{10}Cl_3NO_4$ (290.5): C, 33.07; H, 3.47; N, 4.82. Found: C, 32.55; H, 3.54; N, 5.01.

3.4.3. Methyl-2,2-dimethyl-3-(trichloroacetamido)-propanoate (38). Colorless oil (0.28 g, 74%); R_f 0.53 (petroleum ether/ethyl acetate, 5:1). ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.19 (s, 6H, $2CH_3$), 3.39 (d, J=6.1 Hz, 2H, CH_2), 3.68 (s, 3H, OCH_3), 7.51 (brs, 1H, NH); MS: m/z=276.5. Anal. calcd for $C_8H_{12}Cl_3NO_3$ (276.5): C, 34.74; H, 4.37; N, 5.06. Found: C, 34.67; H, 4.73; N, 4.97.

3.5. Removal of the trichloroacetimido group

The trichloroacetamide derivative **36** (0.5 g, 1.87 mmol) was dissolved in methanol (10 mL) and 2 N KOH (5 mL) and the reaction mixture was refluxed for 1 h. The solvent was evaporated in vacuo and the residue dissolved in dichloromethane (50 mL). The solution was extracted with 1 N NaOH (5×50 mL) and the organic layer dried with magnesium sulfate and concentrated in vacuo to give **24**[37] (see above).

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Five new derivatives of nonactic and homo-nonactic acids from *Streptomyces globisporus*

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Abstract—In addition to the known compounds of the type of nonactic and homononactic acids and their lactones, dilactones and tetralactones, five new compounds, namely homononactyl-nonactoate, a dilactone consisting of nonactic and homononactic acids and three cyclic trimers with nonactic and homononactic acids, were isolated from a strain of *Streptomyces globisporus*. Their structures, including the absolute configurations of the hydroxyl and methyl groups, were determined by extensive spectroscopic techniques such as UV, IR, MS, 1D and 2D NMR.

1. Introduction

Macrotetrolides exhibit a very wide range of effects, ranging from antimicrobial to insecticidal, acaricidal (miticidal), antiprotozoan (coccidiostatic) and antiparasitic (anthelminthic).[1] Their newly described immunosuppressive activity[2] has important consequences for medicine (transplantations, treatment of autoimmune diseases). Nonactin, monactin, dinactin, trinactin and tetranactin isolated from a variety of *Streptomyces* species are cyclotetralactones derived from nonactic (**1**) acid and homononactic (**2**) acid as building units of ionophoretic character. With the exception of nonactin, they exhibit, in addition to antibacterial and antifungal activity, also remarkable acaricidal, insecticidal, coccidiostatic and anthelminthic effects.[1]

Nonactic and homononactic acids are plant growth stimulators and exhibit specific insecticidal effects.[3] There are reports in the literature on the biological effects of a mixture of macrotetrolides (polynactin) or their components (especially tetranactin). The biological activity of nonactic acids has been reported only infrequently, whereas that of their homologs (macrotetrolides G, D, C, and E and isodinactin or isotrinactin) was not tested at all.

This work is part of an on going study[4] performed concerned with the isolation and identification of new antibiotics produced in cultures of different species of the genus *Streptomyces*. In our screening studies for new products of pesticidal compounds[1] we isolated soil microorganisms *S. globisporus* and *S. griseus* from which we obtained the macrotetrolides—nonactin, monactin, dinactin and trinactin by HPLC on normal phase.[5,6] Free nonactic and homononactic acids were isolated from the strain *S. griseus* by RP-HPLC.[7]

For the identification of metabolites containing nonactic and homonactic acids we employed LC-MS/APCI, as described previously.[8] By using gradient elution and highly effective column (~26,500 plates/25 cm), we could separate and identify five new compounds (homononactyl-nonactoate, bilactone consisting of nonactic and homononactic acids and three cyclic trimers with nonactic and homononactic acids), in addition to 12 compounds that had been described previously.

2. Results and discussion

A mixture of antibiotics were isolated from a strain of *S. globisporus*.[6] After repeated crystallization of the major part of the nonactin, monactin, dinactin, and trinactin mixture, the mother liquors were separated by means of semipreparative HPLC on normal phase and two main fractions were obtained. One of them contained compounds without a free carboxyl group (lactones), whereas the other group included compounds with a single free carboxyl group. By further chromatography on RP-HPLC it was possible to obtain a total of 12 compounds. Of them lactone

Keywords: *Streptomyces globisporus*; Nonactic acid; Homo-nonactic acid; Dilactone; Trilactones.
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Table 1. NMR data for dilactone (**3**)

No	^{1}H	^{13}C
1	—	174.1 C
2	2.63 (1H, dq, *J*=9.8, 6.7 Hz)	43.1 CH
2′	1.12 (3H, dd, *J*=2.7;[a] 6.7 Hz)	12.8 CH_3
3	3.99 (1H, dddq, *J*=10.0, 9.8, 7.0, 2.7[a] Hz)	79.9 CH
4a	1.81 (1H, m)	26.9 CH_2
4b	1.62 (1H, m)	
5a	1.97 (1H, m)	31.6 CH_2
5b	1.41 (1H, m)	
6	3.95 (1H, m)	72.2 CH
7a	1.48 (1H, ddd, *J*=14.0, 11.3, 3.4 Hz)	41.9 CH_2
7b	1.81 (1H, ddd, *J*=14.0, 12.1, 3.5 Hz)	
8	4.91 (1H, ddq, *J*=11.3, 3.5, 6.4 Hz)	67.9 CH
8′	1.25 (3H, d, *J*=6.4 Hz)	20.0 CH_3
9	—	174.3 C
10	2.58 (1H, qd, *J*=6.9, 9.9 Hz)	44.2 CH
10′	1.09 (3H, dd, *J*=2.7,[b] 6.9 Hz)	13.1 CH
11	4.02 (1H, dddq, *J*=9.4, 7.0, 9.9, 2.7[b] Hz)	79.8 CH
12a	1.86 (1H, m)	27.0 CH_2
12b	1.65 (1H, m)	
13a	1.98 (1H, m)	31.1 CH_2
13b	1.43 (1H, m)	
14	3.88 (1H, m)	70.5 CH
15a	1.61 (1H, m)	39.7 CH_2
15b	1.86 (1H, m)	
16	4.91 (1H, m)	72.8 CH
16a′	1.28 (1H, m)	30.2 CH_2
16b′	1.37 (1H, m)	
16″	0.88 (3H, t, *J*=7.0 Hz)	9.1 CH_3

[a] $^4J_{\text{H-3,H-2'}}$.
[b] $^4J_{\text{H-11,H-10'}}$.

of nonactic and homonactic acids,[9] dilactone of bis-nonactic[10] and bis-homononactic acids[11] and of course, also the group of tetralactones[12] (nonactin–tetranactin) have previously been described. Dilactone (**3**) and three trilactones (**4**-**6**) containing nonactic and homonactic acids were obtained as new compounds. In the second group (with free hydroxyl group), homononactyl-nonactate (**7**) was newly reported, in addition to the known compounds nonactyl-nonactoate,[13] nonactyl-homononactoate[14] and homononactyl-homononactoate.[14]

Compound **3** was homogeneous by LC-MS/APCI and appeared as pale yellow oil, soluble in non-polar solvents. The UV spectrum of **3** in isopropanol showed only a terminal absorption (at λ_{max} 208 nm), implying that conjugated double bonds are absent in the molecule. The IR spectrum revealed only the presence of an ester (1740 cm^{-1}) and ether functional groups (1070 and 1040 cm^{-1}). The mass spectrum showed a pseudomolecular ion at *m*/*z* 383.2437, which is consistent with a molecular formula of $C_{21}H_{34}O_6$ (Δ 0.4 ppm).

The ^{1}H NMR spectrum (Table 1) of the dilactone (**3**) in $CDCl_3$ indicated the presence of 33 protons. It was very similar to that of the macrolides,[10,11] but a few of the resonances and splitting patterns were different.

The ^{1}H NMR and ^{13}C NMR were extensively analyzed by ^{1}H–^{1}H NOESY and ^{1}H^{13}C HMQC with the aid of proton spin decoupling, thus all of the carbons and protons in the molecule could be assigned and the two partial structures I and II were deduced, as shown in Figure 1. Six oxygen atoms in the molecule were assigned to four of the two ester groups (^{13}C NMR: δ 174.1 (s), 67.9 (d), 174.3 (s), 72.8 (d) and two ethereal oxygen atoms, because of no OH absorption in the IR spectrum and no other carbonyl signal in the ^{13}C NMR spectrum. Two ester groups were also ascertained by hydrolysis of the compound with NaOH to afford two acids (nonactic and homononactic, respectively).

These two partial structures were constructed to build up the plain structure of the dilactone. NOE experiments showed the spatial proximity between two protons in three pairs, that is, H-4/H5 and H-11/H-14, in every pair the two protons were connected through five covalent bonds, thus the presence of two tetrahydrofuran rings was suggested. This suggestion was confirmed by high $^1J_{CH}$ values of C-4/H-4 (132.4 Hz), C-5/H-5 (134.0 Hz), C-11/H-11 (132.9 Hz), and C-14/H-14 (134.3 Hz), all of which were the characteristic *J* values of tetrahydrofuran ring.[15] Since the molecule consisted of two parts, I and II, which were connected by two ester bonds, the C_1-carbonyl of I should bind with the C_{16}–O– of II, and the C_9-carbonyl of II with the C_8–O– of I, respectively. Thus, a sixteen membered macrodiolide ring was deduced, and the plain structure of the dilactone was built up as shown in Figure 1. In order to confirm the proposed structure, the products of hydrolysis, nonactic and homononactic acids, were extensively analyzed by mass fragmentation and methyl ester derivatives by ^{1}H–^{1}H COSY. The specific assignments (Table 1) were tentatively made in comparison with the data reported for tetranactin, nonactin and macrodiolide antibiotics.[10,16,17]

The relative stereochemistry of **3** was detected by 2D-NOESY experiments as shown in Figure 1. Relevant NOE effects were measured between H-2/H-4a (H-10/H-12a), H-3/H-4b (H-11/H-12b), H-3/H-5b (H-11/H-13b), H-4b/H-6 (H-12b/H-14) as well as H-5b and H-6 (H-13b/H-14), but no effect was observed between H-3/H-4a (H-11/H-12a) and H-6/H-8 (H-14/H-16). On the basis of the measured values of the signals for the 2-methyl and 9-methyl groups, we assume that our compound has a relative configuration[10] of 2*R**, 3*R**, 6*S**, 8*S** in accordance with those reported for nonactic and homononactic acids.[10,18]

The *cis*-substituents at α,α'-positions of two tetrahydrofuran rings were shown by NOE enhancements between H-3/H-6, and H-11/H-14, respectively, indicating that the H-3, H-6, H-11, and H-14, should be disposed to the up side of the macrodiolide ring. The stereochemistry at C-2, and C-10, was determined by respective NOE enhancement and *J* values (calculated by MM2 method $J_{2,3}$=10.2 Hz, observed $J_{2,3}$=9.8 Hz, calculated $J_{10,11}$=10.1 Hz, observed $J_{10,11}$=9.9 Hz, respectively, see Table 1). The structure of the dilactone with the relative stereochemistry has thus been elucidated as shown in Figure 1. The absolute stereochemistry of dilactone is described below.

Saponification followed by esterification of compound **3** resulted in two products whose proton NMR data were consistent with those of methyl nonactate and homononactate. Both methyl esters are known to be optically active compounds. Our two compounds were also optically active, which suggests that the compound consists of a mixture of methyl (+)-nonactate and methyl (+)-homononactate. The compounds (**4**, **5**, and **6**) were produced in

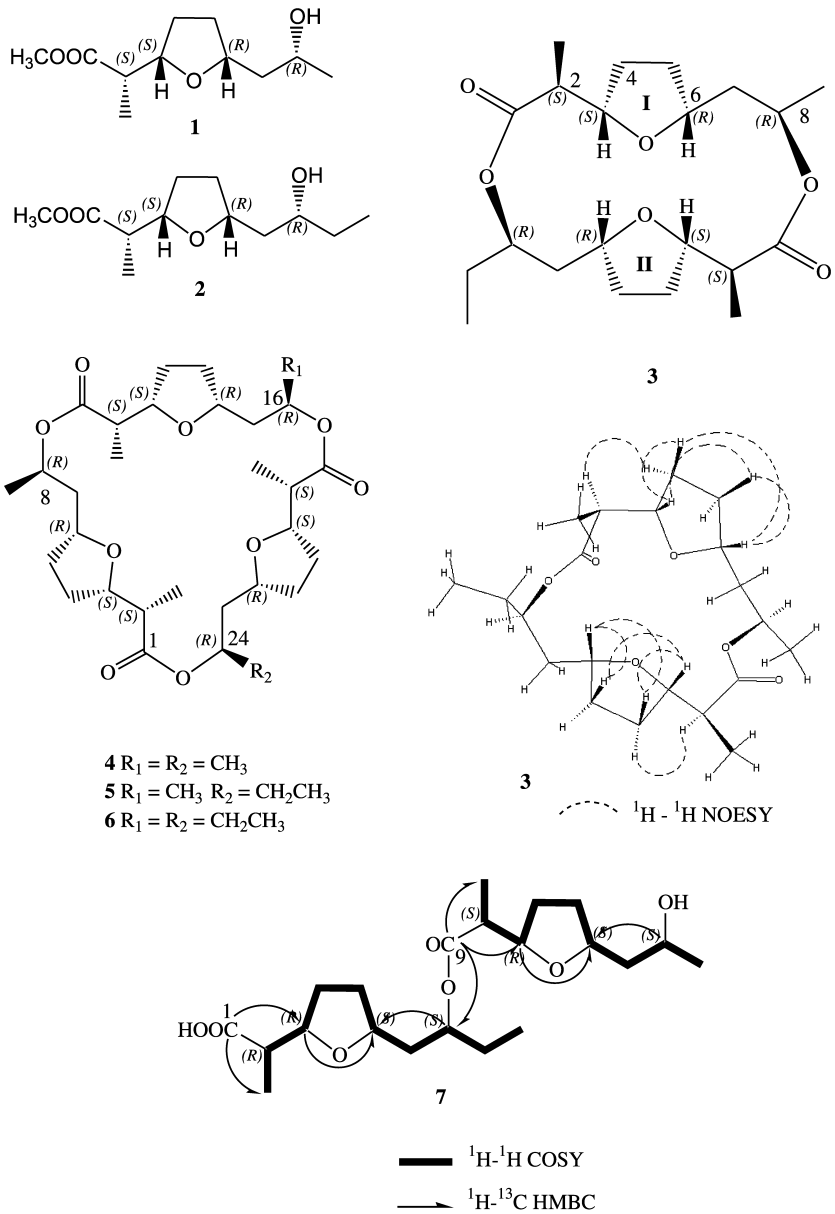

Figure 1. The structures of dilactone consisted of nonactic and homononactic acids (**3**), three cyclic trimers (**4**-**6**) with nonactic and homononactic acids, and homononactyl-nonactoate (**7**) from *Streptomyces globisporus*.

substantial quantities and represent the bulk of the oligolactone components. They were easily separated from each other and purified by preparative reverse phase chromatography.

Structure assignments of these lactones were based on the interpretation of spectroscopic data, especially those from MS and NMR analysis. The structure of **4** was recognized as a macrocyclic trilactone inferred from a set of proton/carbon NMR signals at δ 4.90/68.6. In addition, the LC-MS/APCI spectrum revealed a dominant $[M+Na]^+$ ion peak at *m*/*z* 575. The molecular formula of $C_{30}H_{48}O_9$ was established by HRFAB mass spectrometry, as $[M+H]^+$. As new NMR signals at 1.25 (d) and 20.3 ppm (q) replaced the signals for the ethyl group found in the dilactone (**3**), it was apparent that **4** contained three methyl groups and its structure was therefore consistent with the macrocyclic trilactone shown in Figure 1. The literature NMR data revealed similarity with nonactin and dilactone.[6,11] The difference between **4**, **5**, and **6** was indicated by the molecular weight of **5** and **6** (566 vs. 580) that suggested the increase of the methylene group(s). A thorough NMR analysis of **5** uncovered that this compound is a homologue of **4**.

The structure of **5** was determined as follows: a molecular formula of $C_{31}H_{50}O_9$ was established by HRFAB mass spectrometry. However, the ^1H and ^{13}C NMR spectra revealed signals and correlations for only 21 carbon atoms, indicating two nonactic and one homononactic group. Consequently, **5** had to consist of three units, and these moieties were arranged asymmetrically as illustrated in Figure 1.

Similarly, the molecular formula of **6** was based on its molecular ion $[M+H]^+$ (*m*/*z* 581.3693) as determined by HRFABMS, invoking the molecular formula of $C_{32}H_{52}O_9$.

The ^{1}H and ^{13}C NMR signals of **6** were remarkably similar to those of **5**. Again, the ^{1}H and ^{13}C NMR spectra of **6** accounted for only 22 carbon atoms derived from one nonactic acid linked to two homononactic groups. While only the signals for the protons in position 16′ (H-16′a,b) in **6** appear as multiplets at δ 1.30 and 1.37, the signals for the same protons were not located in **5**. However, the protons (H-24′a,b) for both, **5** and **6**, appear as multiplets, and resonate at δ 1.29 (H-24′a) and δ 1.38 (H-24′b) for **5** and at δ 1.31 (H-24′a) and δ 1.40 (H-24′b) for **6**, respectively. The NMR spectra of **6** suggested the presence of two units of homononactic acid and one unit of nonactic acid. Given the molecular formula, **6** must exist in the form of an asymmetric trimer as depicted in Figure 1.

The absolute configurations of the oligolactones were deduced from the negative rotation of two isolated constituents (nonactic and homononactic acids). The optical rotation of both compounds (**1** and **2**), hydrolytically prepared from **5** or **6** gave $[\alpha]_D^{25}=+14.6$ (*c* 0.12, $CHCl_3$) and $[\alpha]_D^{25}=+17.2$ (*c* 0.12, $CHCl_3$), respectively. These values were nearly identical with those previously published.[15,19] When considering that nonactic and homononactic acids were present in **5** as well as in **6**, it can be deduced that the absolute stereochemistry of the isolated oligolactones is as indicated in Figure 1.

The molecular formula of **7** was determined to be $C_{21}H_{36}O_7$ on the basis of high-resolution FABMS data. The IR spectrum showed absorption bands at 1740 cm^{-1}, indicating the presence of an ester group. The ^{1}H and ^{13}C NMR spectra of **7** in $CDCl_3$ are summarized in Table 4. The ^{13}C NMR spectrum of **7** showed 21 carbon signals, which were assigned to four methyl groups, seven methylenes, eight methines, and two quaternary carbons by DEPT experiments. The latter observation together with the absence of sp^2 hybridized carbons associated with double bond(s) accounted for four sites of unsaturation. Two of the four sites of unsaturation belong to two carbonyl atoms (carboxylic acid at δ 177.4 ppm and ester at 174.4 ppm). These observations required for the acid **7** to be bicyclic.

Analysis of the 2D NMR COSY data for **7** revealed two diagnostic correlation sequences; the first from H-2′ to H-8″ and the second from H-10′ to H-16′ (Fig. 1). Furthermore, HMBC correlations from C-9 to H-8 permitted connection of both substructural units, as show in Figure 1. The relative and absolute stereochemistry of both subunits (nonactic and homononactic acids) was determined after alkaline hydrolysis. Unfortunately, as described previously in two naturally occurring dimers, nonactyl nonactate[13] and bonactin,[14] also in our case it was not possible to find optically active nonactic and homomonactic acids. However, these results are in contradiction with the values found by us with cyclic isomers.[1]

In agreement with the literature data,[1] all four lactones isolated by us exhibit a significant activity against both Gram-negative and Gram-positive bacteria and also against fungi (Table 5). It is assumed that the biological activity of tetralactones (from nonactin to tetranactin) is connected with chelatation by alkali metal ions,[20] by sodium in particular. Although the compounds described in this paper are di- and trilactones, they exhibit biological activity comparable to that of nonactin.[1] After all, it is not surprising in view of the fact that even the previously described monolactones and dilactone had considerable antimicrobial activity.[9,10]

Literature data on two linear dimers, that is, nonactylnonactate and bonactin, are contradictory. The former did not exhibit antimicrobial activity[13] up to 2 mg/ml, whereas the latter exhibited excellent activity[14] at a concentration of 1 mg/ml.

As compared with previously tested organisms, this time we also used brine shrimp (*Artemia salina*). Due probably to a high sodium complex formation, the effects of, for example, trilactone (**5**), were nearly fatal with LC_{50}=2 ng/ml (Table 5).

3. Conclusion

All the compounds identified and described in this paper contained nonactic and/or homonactic acid. We assume that the individual lactones are by-products of biosynthesis or even biosynthetic intermediates. This assumption seems to be confirmed by their optical activity, which was detected in all four lactones (one dilactone and three trilactones). On the other hand, in case of the linear dimer the situation is not clear, which is in spite of the fact that the two previously isolated dimers have been considered natural compounds.

4. Experimental

4.1. General

UV spectra were measured by a Cary 118 (Varian) apparatus in MeOH in the range 200–350 nm. A Perkin–Elmer Model 1310 (Perkin–Elmer, Norwalk, CT) infrared spectrophotometer was used for scanning infrared spectroscopy of methyl esters as neat film. NMR spectra were recorded in a Bruker AMX 500 spectrometer (Bruker Analytik, Karlsruhe, Germany) at 500.1 MHz (^{1}H) and 125.7 MHz (^{13}C). The positive-ion MS/FAB mass spectra were recorded in a VG 7070E-HF spectrometer (Micromass, Manchester, UK).

The LC-MS/APCI was performed as reported previously:[21] briefly: the HP 1090 series (HP 1090 series, Hewlett–Packard, USA) was used with two columns (HIRPB-250AM 250×2.1 mm ID, 5 μm phase particle, ~26,500 plates/25 cm). A quadruple mass spectrometer system Navigator (Finnigan MAT, San Jose, CA, USA) was used: vaporizer temperature 400 °C, capillary heater temperature 220 °C, corona current 5 μA, sheath gas high-purity nitrogen, pressure ca. 380 kPa, and auxiliary gas (also nitrogen) flow rate 1500 ml/min. Ions with *m/z* 50–1500 were scanned with a scan time of 0.5 s, flow 0.37 ml/min. Compounds were separated using a solvent program with water–acetonitrile (50:50) to 10 min and linear gradient from 10 to 40 min (100% acetonitrile).

Preparative HPLC separations were accomplished on a

Table 2. ^{1}H NMR data for trilactones (**4**, **5** and **6**)

No	4	5	6
2, 10, 18	2.57 (3H, dq, *J*=9.8, 6.7 Hz)	2.57+2.54 (2H+1H, dq, *J*=9.8, 6.7 Hz)	2.57+2.54 (1H+2H, dq, *J*=9.8, 6.7 Hz)
2′, 10′, 18′	1.10 (9H, dd, *J*=2.7,[a] 6.7 Hz)	1.11 (9H, dd, *J*=2.7,[a] 6.7 Hz)	1.09 (9H, dd, *J*=2.7,[a] 6.7 Hz)
3, 11, 19	4.01 (3H, dddq, *J*=10.0, 9.8, 7.0, 2.7[a] Hz)	4.01 (3H, dddq, *J*=10.0, 9.8, 7.0, 2.7[a] Hz)	4.01 (3H, dddq, *J*=10.0, 9.8, 7.0, 2.7[a] Hz)
4a, 12a, 20a	1.82 (3H, m)	1.80 (3H, m)	1.82 (3H, m)
4b, 12b, 20b	1.63 (3H, m)	1.61 (3H, m)	1.61 (3H, m)
5a, 13a, 21a	1.98 (3H, m)	1.97 (3H, m)	1.98 (3H, m)
5b, 13b, 21b	1.40 (3H, m)	1.42 (3H, m)	1.43 (3H, m)
6, 14, 22	3.90 (3H, m)	3.89 (3H, m)	3.90 (3H, m)
7a, 15a, 23a	1.48 (3H, ddd, *J*=14.0, 11.3, 3.4 Hz)	1.50 (3H, ddd, *J*=14.0, 11.3, 3.4 Hz)	1.49 (3H, ddd, *J*=14.0, 11.3, 3.4 Hz)
7b, 15b, 23b	1.80 (3H, ddd, *J*=14.0, 12.1, 3.5 Hz)	1.81 (3H, ddd, *J*=14.0, 12.1, 3.5 Hz)	1.79 (3H, ddd, *J*=14.0, 12.1, 3.5 Hz)
8, 16, 24	4.90 (3H, ddq, *J*=11.3, 3.5, 6.4 Hz)	4.91 (3H, ddq, *J*=11.3, 3.5, 6.4 Hz)	4.89 (3H, ddq, *J*=11.3, 3.5, 6.4 Hz)
8′ 16′, 24′	1.25 (9H, d, *J*=6.4 Hz)	1.25 (6H, d, *J*=6.4 Hz)[b]	1.25 (3H, d, *J*=6.4 Hz)[c]
16′a, 24′a	—	1.29 (1H, m)[d]	1.30 (1H, m); 1.31 (1H, m)
16′b, 24′b	—	1.38 (1H, m)[e]	1.37 (1H, m); 1.40 (1H, m)
16″, 24″	—	0.89 (3H, t, *J*=7.0 Hz)[f]	0.89 (6H, t, *J*=7.0 Hz)

[a] $^{4}J_{\text{H-3,H-2′; H-11,H-10′; H-19,H-18′}}$.
[b] Values for only 8′, 16′.
[c] Value for only 8′.
[d] Value for only 24′a.
[e] Value for only 24′b.
[f] Value for only 24″.

Discovery C18 column (Supelco) particle size 5 μm, length×I.D. (250 mm×21.2 mm) using a linear gradient from 20% H_2O and 80% acetonitrile to 1% water and 99% acetonitrile over 25 min, with a flow rate of 9.9 ml/min and monitored by a variable wavelength detector at 208 nm. These conditions were used to separate all the compounds in the crude extract.

4.1.1. Esterification. To ~5 mg (0.025 mol) of the ester (lactone) was added 0.1 N KOH, and the resulting mixture was stirred at room temperature for 24 h. The mixture was acidified to pH 2.0 with dilute HCl and extracted three times with ethyl ether (3×10 ml) and after removal of the solvent an oily residue was obtained (~3–4 mg). The resulting acids were dissolved in 5 ml methanol and an etheral solution of CH_2N_2 (1%) was slowly added while swirling the reagent vessel. The reaction was followed by preparative RP-HPLC separations on a Discovery C18 column.

Methyl nonactate (**1**), colorless oil, $[\alpha]_D^{25}$=+14.6 (*c* 0.12, $CHCl_3$); (lit.[22] for (+) isomer, $[\alpha]_D^{25}$=+22.1 (*c* 0.7, $CHCl_3$), for (−) isomer $[\alpha]_D^{25}$=−17.8 (*c* 3.6, $CHCl_3$)[19]); LC-MS/APCI: $[M+H]^+$ *m/z* 217 (100%), $[M+Na]^+$; *m/z* 239, *m/z* 202 (47%) $[M+H-CH_3]^+$; *m/z* 186 (47%) $[M+H-CH_3O]^+$; IR (film) ν_{max} 3600 (OH), 2900, 1740 (COOH), C–O–C (1170 and 1040) cm^{-1}; ^{1}H NMR 1.12 (3H, dd, *J*=2.7, 6.7 Hz, H-2′), 1.25 (3H, d, *J*=6.4 Hz, H-8′), 1.41 (1H, m, H-5b), 1.48 (1H, ddd, *J*=13.9, 10.8, 3.4 Hz, H-7a), 1.62 (1H, m, H-4b), 1.81 (1H, ddd, *J*=13.9, 12.1, 3.7 Hz, H-7b), 1.81 (1H, m, H-4a), 1.97 (1H, m, H-5a), 2.53 (1H, dq, *J*=9.5, 6.7 Hz, H-2), 3.64 (3H, s, OMe), 3.95 (1H, m, H-6), 3.99 (1H, dddq, *J*=9.9, 9.5, 6.7, 2.7 Hz, H-3), 4.91 (1H, ddq, *J*=10.8, 3.7, 6.4 Hz, H-8); ^{13}C NMR 174.5 (C-1, s), 80.1 (C-3, d), 72.5 (C-6, d), 68.1 (C-8, d), 52.3 (Me, q), 42.0 (C-7, t), 31.4 (C-5, t), 27.2 (C-4, t), 19.8 (C-8′, q), 13.0 (C-2′, q).

Methyl homononactate (**2**), (NMR, see lit.[23]) colorless oil, $[\alpha]_D^{25}$=+17.2 (*c* 0.12, $CHCl_3$); (lit.[15] for (−) isomer, $[\alpha]_D^{25}$=−23.7 (*c* 0.14, $CHCl_3$); LC-MS/APCI: *m/z* 231 (100%) $[M+H]^+$; *m/z* 253 (100%) $[M+Na]^+$; *m/z* 202 (43%) $[M+H-C_2H_5]^+$; *m/z* 200 (39%) $[M+H-CH_3O]^+$; IR (film) ν_{max} 3600 (OH), 2900, 1740 (COOH), C–O–C (1170 and 1040) cm^{-1}; ^{1}H NMR 0.88 (3H, t, *J*=7.0 Hz, H-8″), 1.09 (3H, qd, *J*=2.7, 6.9 Hz, H-2′), 1.28 (1H, m, H-8a′), 1.37 (1H, m, H-8b′), 1.43 (1H, m, H-5b), 1.61 (1H, m, H-7a), 1.65 (1H, m, H-4b), 1.86 (1H, m, H-4a), 1.86 (1H, m, H-7b), 1.98 (1H, m, H-5a), 2.55 (1H, qd, *J*=9.4, 6.9 Hz, H-2), 3.65 (3H, s, OMe), 3.88 (1H, m, H-6), 4.02 (1H, dddq, *J*=9.9, 9.4, 7.0, 2.7 Hz, H-3), 4.91 (1H, m, H-8); ^{13}C NMR 174.2

Table 3. ^{13}C NMR data for trilactones (**4**, **5**, and **6**)

No	4	5	6
1	174.2 C	174.2 C	174.2 C
2	43.4 CH	43.4 CH	43.4 CH
2′	12.9 CH_3	12.9 CH_3	12.9 CH_3
3	80.1 CH	80.1 CH	80.1 CH
4	27.6 CH_2	27.6 CH_2	27.6 CH_2
5	31.5 CH_2	31.5 CH_2	31.5 CH_2
6	74.5 CH	74.5 CH	74.5 CH
7	42.4 CH_2	42.4 CH_2	42.4 CH_2
8	68.6 CH	68.6 CH	68.6 CH
8′	20.3 CH_3	20.3 CH_3	20.3 CH_3
9	174.2 C	174.2 C	174.3 C
10	43.4 CH	43.4 CH	45.1 CH
10′	12.9 CH_3	12.9 CH_3	13.0 CH_3
11	80.1 CH	80.1 CH	80.2 CH
12	27.6 CH_2	27.6 CH_2	27.8 CH_2
13	31.5 CH_2	31.5 CH_2	31.4 CH_2
14	74.5 CH	74.5 CH	73.0 CH
15	42.4 CH_2	42.4 CH_2	40.1 CH_2
16	68.6 CH	68.6 CH	69.2 CH
16′	20.3 CH_3	20.3 CH_3	29.5 CH_2
16″	—	—	9.2 CH_3
17	174.2 C	174.3 C	174.3 C
18	43.4 CH	45.1 CH	45.1 CH
18′	12.9 CH_3	13.0 CH	13.0 CH
19	80.1 CH	80.2 CH	80.2 CH
20	27.6 CH_2	27.8 CH_2	27.8 CH_2
21	31.5 CH_2	31.4 CH_2	31.4 CH_2
22	74.5 CH	73.0 CH	73.0 CH
23	42.4 CH_2	40.1 CH_2	40.1 CH_2
24	68.6 CH	69.2 CH	69.2 CH
24′	20.3 CH_3	29.5 CH_2	29.5 CH_2
24″	—	9.2 CH_3	9.2 CH_3

Table 4. ^{1}H and ^{13}C NMR data for linear diester (**7**)

No	^{1}H	^{13}C
1	—	177.4 C
2	2.47 (1H, dq, *J*=7.0, 1.1 Hz)	45.0 CH
2′	1.09 (3H, d, *J*=7.0 Hz)	13.4 CH_3
3	4.00 (1H, m)	80.3 CH
4a	1.92 (1H, m)	28.3 CH_2
4b	1.61 (1H, m)	
5a	1.95 (1H, m)	31.1 CH_2
5b	1.43 (1H, m)	
6	4.03 (1H, m)	76.4 CH
7a	1.55 (1H, m)	40.7 CH_2
7b	1.72 (1H, m)	
8	4.91 (1H, m)	68.9 CH
8a′	1.28 (1H, m)	27.4 CH_2
8b′	1.37 (1H, m)	
8″	0.90 (3H, t, *J*=7.0 Hz)	9.3 CH_3
9	—	174.4 C
10	2.52 (1H, dq, *J*=6.9, 1.2 Hz)	45.5 CH
10′	1.14 (3H, dd, *J*=2.7,[a] 6.9 Hz)	13.2 CH_3
11	4.00 (1H, m)	80.1 CH_2
12a	1.90 (1H, m)	29.0 CH_2
12b	1.62 (1H, m)	
13a	1.91 (1H, m)	31.3 CH_2
13b	1.42 (1H, m)	
14	4.04 (1H, m)	40.8 CH
15a	1.58 (1H, m)	73.4 CH_2
15b	1.76 (1H, m)	
16	5.15 (1H, tq, *J*=6.8 2.9 Hz)	31.3 CH
16′	1.24 (3H, d, *J*=6.8 Hz)	20.4 CH_3

[a] $^{4}J_{H\text{-}11,H\text{-}10'}$.

(C-1, s), 80.0 (C-3, d), 73.0 (C-8, d), 70.6 (C-6, d), 53.0 (Me, q), 44.5 (C-2, d), 40.1 (C-7, t), 30.8 (C-5, t), 30.4 (C-8′, t), 27.2 (C-4, t), 13.4 (C-2′, q), 9.7 (C-8″, q).

The following known compounds were identified in mother liquor—lactone of nonactic acid (*m/z* 207 $[M+Na]^+$); lactone of homonactic acid (*m/z* 221 $[M+Na]^+$); dilactone of bis-nonactic acids (*m/z* 391 $[M+Na]^+$); dilactone bis-homononactic acids (*m/z* 419 $[M+Na]^+$); nonactyl-nonactoate (*m/z* 409 $[M+Na]^+$); nonactyl-homononactoate (*m/z* 423 $[M+Na]^+$); homononactyl-homononactoate (*m/z* 437 $[M+Na]^+$); nonactin (*m/z*759 $[M+Na]^+$); monactin (*m/z* 773 $[M+Na]^+$); dinactin (*m/z* 787 $[M+Na]^+$); trinactin (*m/z* 801 $[M+Na]^+$); tetranactin (*m/z* 815 $[M+Na]^+$). The mass spectra (LC-MS/APCI) of the above-mentioned compounds agreed with previously published data.

The newly reported compounds are described below:

Compound **3** is pale yellow oil, yield 14.3 mg; $[\alpha]_D^{25}=+12.1$ (*c* 0.11, EtOH); IR (film) ν_{max} 3600 (OH), 2900, 1740 (COOH), C–O–C (1070 and 1040) cm^{-1}; HRFABMS (*m/z*) 383.2437 $[M+H]^+$, (Calcd for $C_{21}H_{35}O_6$ *m/z* 383.2433), (Δ 0.4 ppm); LC-MS/APCI: *m/z* 383 $[M+H]^+$, *m/z* 405 $[M+Na]^+$, *m/z* 185 [monomeric A+H–H_2O]$^+$; *m/z* 199 [monomeric B+H–H_2O]$^+$, A is fragment of nonactic acid, B is fragment of homononactic acid; NMR data, see Table 1.

Compound **4** is slightly yellow oil, yield 5.8 mg; $[\alpha]_D^{25}=+14.5$ (*c* 0.09, EtOH); IR (film) ν_{max} 3600 (OH), 2900, 1740 (COOH), C–O–C (1170 and 1040) cm^{-1}; HRFABMS (*m/z*) 553.3381 $[M+H]^+$, (Calcd for $C_{30}H_{49}O_9$ *m/z* 553.3376), (Δ 0.5 ppm); LC-MS/APCI: *m/z* 553 $[M+H]^+$, *m/z* 575 $[M+Na]^+$, *m/z* 369 [dimeric fragment of 2xA+H–H_2O]$^+$, *m/z* 185 [monomeric fragment A+H–H_2O]$^+$; ^{1}H NMR data, see Table 2, ^{13}C NMR data see Table 3.

Compound **5** is pale brown oil, yield 9.1 mg; $[\alpha]_D^{25}=+9.8$ (*c* 0.16, EtOH); IR (film) ν_{max} 3600 (OH), 2900, 1740 (COOH), C–O–C (1170 and 1040) cm^{-1}; HRFABMS (*m/z*) 567.3537 $[M+H]^+$, (Calcd for $C_{31}H_{51}O_9$ *m/z* 567.3533), (Δ 0.4 ppm); LC-MS/APCI: *m/z* 567 $[M+H]^+$, *m/z* 589 $[M+Na]^+$, *m/z* 383 [dimeric fragment of A+B+H–H_2O]$^+$, *m/z* 369 [dimeric fragment of 2xA+H–H_2O]$^+$, *m/z* 199 [monomeric fragment of B+H–H_2O]$^+$, *m/z* 185 [monomeric fragment A+H–H_2O]$^+$; ^{1}H NMR data, see Table 2, ^{13}C NMR data see Table 3.

Compound **6** is pale yellow oil, yield 3.1 mg; $[\alpha]_D^{25}=+19.0$ (*c* 0.15, EtOH); IR (film) ν_{max} 3600 (OH), 2900, 1740 (COOH), C–O–C (1170 and 1040) cm^{-1}; HRFABMS (*m/z*) 581.3693 $[M+H]^+$, (Calcd for $C_{32}H_{52}O_9$ *m/z* 581.3689), (Δ 0.4 ppm); LC-MS/APCI: *m/z* 581 $[M+H]^+$, *m/z* 603 $[M+Na]^+$, *m/z* 398 [dimeric fragment of B+B+H–H_2O]$^+$, *m/z* 383 [dimeric fragment of A+B+H–H_2O]$^+$, *m/z* 199 [monomeric fragment of B+H–H_2O]$^+$, *m/z* 185 [monomeric fragment A+H–H_2O]$^+$; ^{1}H NMR data, see Table 2, ^{13}C NMR data see Table 3.

Compound **7** is colorless oil, yield 19.2 mg; $[\alpha]_D^{25}=+5.3$ (*c* 0.10, EtOH); IR (film) ν_{max} 3600 (OH), 2900, 1740

Table 5. Biological activities of derivatives (**3**-**7**) and standards

Compound	Test organism				
	Staphylococcus aureus[a]	*Bacillus subtilis*[a]	*Escherichia coli*[a]	*Saccharomyces cerevisiae*[a]	*Artemia salina*[b,c]
3	57.2±7.2[d]	81.2±4.6	<0.5	<0.5	41.3±7.5
4	28.9±4.4	37.6±3.6	<0.5	<0.5	5.2±0.6
5	56.3±3.4	31.7±5.3	<0.5	<0.5	2.0±0.6
6	71.8±5.3	26.5±3.2	<0.5	<0.5	4.9±0.5
7	43.9±5.6	57.0±2.8	<0.5	<0.5	35.0±3.1
Ivermectin	<0.5	<0.5	<0.5	<0.5	2.5±0.5
Penicillin G	91.6±11.2	65.3±2.4	<0.5	<0.5	>1000
Streptomycin	<0.5	<0.5	75.8±3.4	<0.5	>1000
Amphotericin B	<0.5	<0.5	<0.5	76.2±1.2	>1000

[a] Samples (10 μg) were applied to 6.3 mm paper disks; values are diameters (mm) of inhibitory zones.
[b] In ng/ml (LC_{50}).
[c] The details are in the Section 4.
[d] The drug potencies were determined and the values represent values (mean±SD) from five independent observations.

(COOH), C–O–C (1170 and 1040) cm^{-1}; HRFABMS (*m/z*) 401.2537 $[M+H]^+$, (Calcd for $C_{21}H_{37}O_7$ *m/z*401.2539), (Δ 0.2 ppm); LC-MS/APCI: *m/z* 401 $[M+H]^+$, *m/z* 423 $[M+Na]^+$, *m/z* 199 [monomeric fragment of $B+H-H_2O]^+$; *m/z* 185 [monomeric fragment $A+H-H_2O]^+$; NMR data, see Table 4.

4.2. Biological activity

Antibacterial and antifungal assays were carried out according to our previous paper.[24] The test organisms were from the Czechoslovak Collection of Microorganisms, Brno. The amount of the compound was 10 μg per test disk (see Table 5).

The sample (~0.05 mg) was dissolved in 50 μl of DMSO and added to a vial of artificial seawater (3.0 ml). Approximately 20 brine shrimp, *Artemia salina*, were added to the vial and then observed periodically over a 24 h period. A positive assay was the death of 50% brine shrimps.[25] Compounds listed in Table 5 were used as controls.

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Synthesis and structural analysis of new macrocycles exhibiting 3,9-dimethyl-3,9-diaryl-2,4,8,10-tetraoxaspiro[5.5]undecane units

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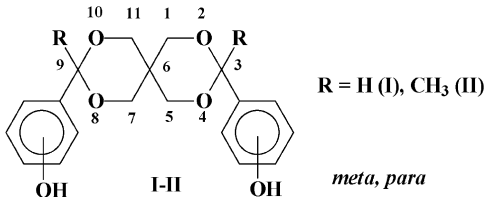
Abstract—The template synthesis of a new series of macrocycles (from monomers to tetramers) with 2,4.8,10-tetraoxaspiro[5.5]undecane units is reported. The structural analysis of the compounds is carried out using the data of high field NMR investigations, mass spectrometry studies (FAB, MALDI and ESI-MS) and the solid state X-ray diffractometry molecular structures for three compounds.

1. Introduction

The development of the synthesis and structural analysis of macrocycle compounds includes the use of this type of derivatives in chiral recognition processes, in the discrimination and separation of enantiomers and in the catalysis of enantioselective reactions.[1] The synthesis of macrocycles with enantioselective and enantiospecific supramolecular proprieties is based on chiral substrates in many cases proceeding from natural compounds. The macrocyclisation of sugars (e.g., with polyethyleneglycols) leads to crown ethers exhibiting high coordination ability and selectivity.[2–8] In order to obtain compounds with similar proprieties but with various cavities and coordination abilities some peculiar chiral substrates as bicyclo and spiro derivatives of saturated heterocycles with six-membered rings were successfully used.[9–20] Important features in high yield macrocyclisation reactions are the geometry of the substrate, which has to exhibit the pre-organization required by the incorporation in the macrocycle, and the high number of heteroatoms which can coordinate to cations and are able to promote the macrocyclisation by the template effect.[21] In order to identify suitable substrats for macrocyclization, we analyzed the stereochemistry of spiro-1,3-dioxane derivatives



I-II

Scheme 1.

(I and II) exhibiting 2,4,8,10-tetraoxaspiro[5.5]undecane skeleton and aromatic substituents (phenol groups) at the extremities (positions 3 and 9) of the spirane (Scheme 1).

The spirane skeleton (I–II) is chiral and shows the characteristic helical and axial chirality of spiro compounds with six-membered rings[22–24] and the two 1,3-dioxane rings of the spirane exhibit a favorable angular orientation. The six-membered rings are anancomeric, the substituents in the acetal part of the 1,3-dioxane ring have high A-values and are efficient 'holding groups'.[25] The stereochemistry of these compounds (I and II) is different if the aromatic groups are the unique substituents at positions 3 and 9 (R=H, I) or if besides the aromatic substituents, methyl groups are also located at the same positions (R=CH_3, II). These differences were previously observed in the investigations on the more simple structures of 2-aryl-1,3-dioxanes III and 2-alkyl,2-aryl-1,3-dioxanes IV. In the first case (Scheme 2) the aromatic groups, due to their high *A*-values (e.g., A_{Ph}=3.12 kcal/mol),[26] prefer the equatorial orientation (conformer IIIA), while in the second case the conformational equilibrium is strongly shifted towards the conformer exhibiting the aromatic substituent in axial

Keywords: Macrocycle; Spiro-1,3-dioxane; X-ray diffractomatry; ESI-MS; Ditopic ligand.
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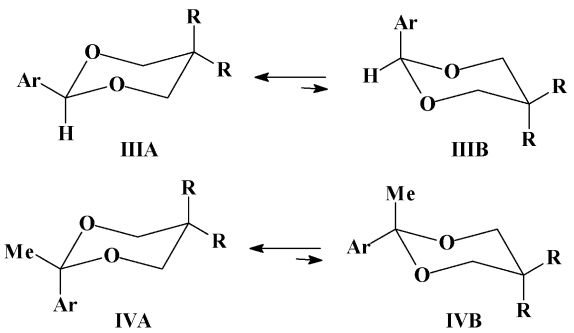


Scheme 2.

orientation (IVA). The preference of the aromatic group for the axial orientation in this case is about three times higher (Ar=C_6H_5; $\Delta G°_{IVB-IVA}$=2.43 kcal/mol)[26] than calculated using the A-values of methyl and phenyl groups ($\Delta G°$calcd=$A_{Me}-A_{Ph}$=3.98−3.12=0.86 kcal/mol).[25]

In agreement with these data and with the results of the investigations on the stereochemistry of similar spirane derivatives[27,28] the equatorial orientation of both aromatic groups in compounds I and the axial orientation of the aromatic substituents in compounds II was predicted. The enclosure of macrocycles (promoted by the orientation of the 1,3-dioxane rings of the spirane) starting from I is performed by the connection of equatorial groups (equatorial–equatorial connection) of the starting substrate, while the macrocyclisation of compounds II occurs between the axial substituents of the substrate (axial–axial connection). The macrocyclisation of I and II leads to cavities with different dimensions and geometries.

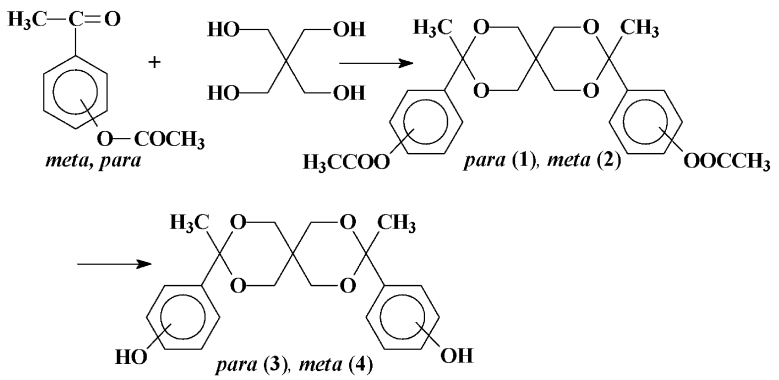
In a recent work[29] the efficient synthesis of new coronands of various sizes (monomers and dimers) with equatorial–equatorial cyclisation in the macrocycles, starting from 3,9-di(*meta*-hydroxyphenyl)-2,4,8,10-tetraoxaspiro[5.5]-undecane and derivatives of different polyethyleneglycols (from mono to hexa) was reported.

In this work we describe the design, synthesis, NMR, single crystal X-ray diffraction based analysis and the ESI-MS investigations of a series of macrocycles (with axial–axial connection) obtained from spiro-1,3-dioxanes **3** and **4** (Scheme 3) bearing axial aryl groups at the extremities of the spirane. The starting spiranes **3** and **4** were obtained[30] by usual procedures[31] using the acetalisation of pentaerythritol with protected hydroxyketones (Scheme 3).

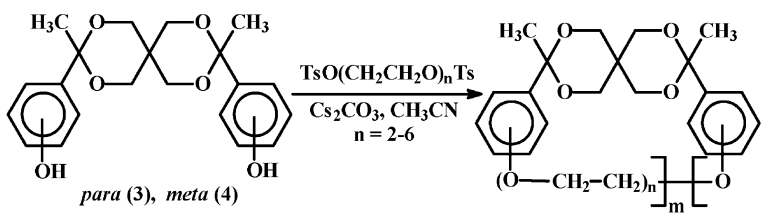
The axial disposition of the aromatic groups in the target macrocycles determines a peculiar behavior and shape for the created cavities. The structural differences among the macrocycles with axial–axial connection of the spirane units and of those with equatorial–equatorial connection of the spirane skeleta (previously reported[29]) determine a priori differences among the ability and the selectivity of the possible complexation processes involving the two types of macrocycles and motivate the interest for this work.

2. Results and discussion

New macrocycles **5**-**11** exhibiting spirane units were obtained by the cyclisation of compounds **3** and **4** with several ditosylated polyethyleneglycols (Scheme 4).



Scheme 3.



para:	n=2, m=2,3,4	5b, 5c, 5d
	n=3, m=2	6b
	n=4, m=1,2,3,4	7a, 7b, 7c, 7d
	n=5, m=1,2,3,4	8a, 8b, 8c, 8d
	n=6, m=1,2,3,4	9a, 9b, 9c, 9d
meta:	n=2, m=2	10b
	n=3, m=1,2	11a, 11b

Scheme 4.

Table 1. Results in the synthesis of macrocycles **5**-**11**

Compound	*N*	Isomer	Global yields[a]	Observed macrocycles (yields, %, of separated terms)
5	2	*para*	53	Dimer (24), trimer, tetramer (2)
6	3	*para*	34	Dimer (34)
7	4	*para*	41	Monomer (6), dimer (18), trimer, tetramer
8	5	*para*	56	Monomer (20), dimer (22), trimer, tetramer
9	6	*para*	61	Monomer (17), dimer (15), trimer, tetramer
10	2	*meta*	27	Dimer (27)
11	3	*meta*	32	Monomer (15), dimer (17)

[a] The global yields were calculated using the amounts of macrocycles, single terms and mixture of terms, isolated by flash-chromatography.

The reactions were performed in good yields (27–61%, Table 1), using Cs_2CO_3 as base and template and acetonitrile as solvent.

The reactions gave rise to monomer, dimer, trimer and tetramer macrocycles (proved by mass spectrometry). The mixtures were very complex. However, after many chromatography separations all the monomers and all the dimers could be isolated as single compounds and their structures could be determined using high field NMR (500 and 600 MHz) spectroscopy, mass-spectrometry (FAB, MALDI and ESI-MS) and single crystal X-ray diffractometry. The tetramer **5d** was also isolated as a single compound, but in the other cases of larger cycles (trimers and tetramers) column chromatography separations led only to enriched mixtures of the target compounds. Because during the chromatography separations many fractions containing mixtures of compounds were collected, a quantitative appreciation of the ratios of different compounds could not be calculated. HPLC investigations for compounds **8** and **9** made it possible to establish the ratios of monomers, dimers and trimers in the crude products. For **8** the ratio monomer ($t_{R(m)}$=4.7 min)/dimer ($t_{R(d)}$=8.2 min)/trimer ($t_{R(t)}$=16.2 min) is 48/44/8, while the ratio of monomer ($t_{R(m)}$=5.3 min)/dimer ($t_{R(d)}$=9.6 min)/trimer ($t_{R(t)}$=20.6 min) in the case of compound **9** was found to be 50/45/5.

The preference in the macrocyclisation reaction for the different size macrocycles can be correlated with the lengths of the polyethyleneglycol chains and with the *para* or *meta* positions of the reacting groups on the aromatic rings. In the *para* series if the chain is long enough (n=4–6) all the rings are formed (monomer–tetramer). The monomers and the dimers are obtained in comparable amounts and they are the main products of the reactions. In the *meta* series for n=2 only the dimer macrocycle was formed, while for the longer chain (n=3) the crude product exhibits monomer and dimer compounds in comparable amounts.

2.1. Solid state molecular structures

The molecular structures for monomers **8a**, **9a** and for dimer **5b** were obtained by single crystal X-ray diffractometry. The ORTEP diagrams (Figs. 1–3) show the axial orthogonal orientation of all aromatic rings. The orthogonal disposition of the aromatic rings is deduced from the values of the dihedral angles formed by the aromatic rings and the best plane of the corresponding 1,3-dioxane rings (Table 2).

The X-ray diffractometry investigations for **9a** revealed the presence in the crystal of two different molecules (with close structures). Each macrocycle exhibits a molecule of water included in its cavity and shows a disorder of the part of the chain involved in the fixation of water. The distances from the oxygen atom of the included molecule of water to the closer oxygen atom of the chain are of d=2.598 and 2.781 Å, respectively and suggest the fixation of water by

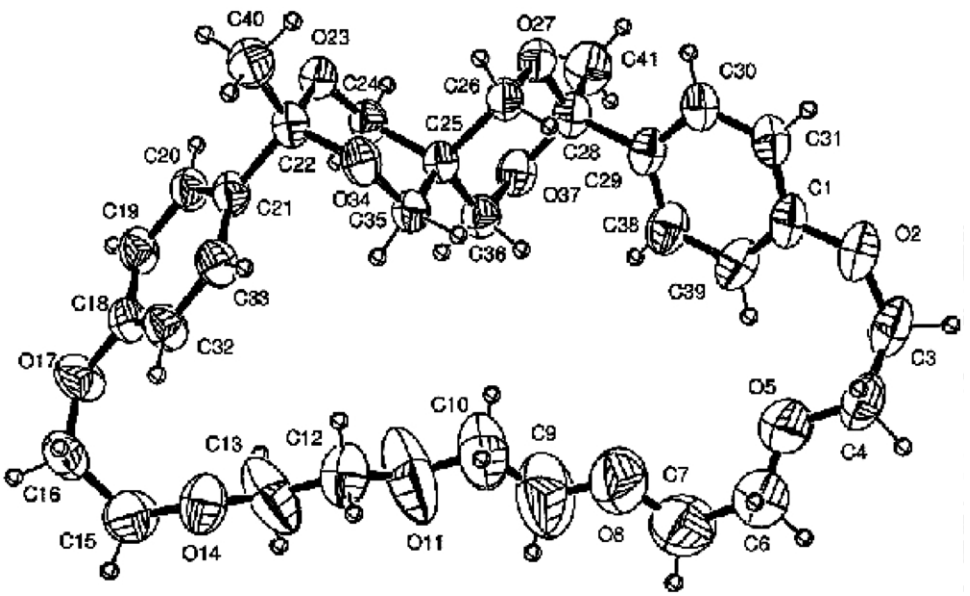


Figure 1. ORTEP diagram of compound **8a**.

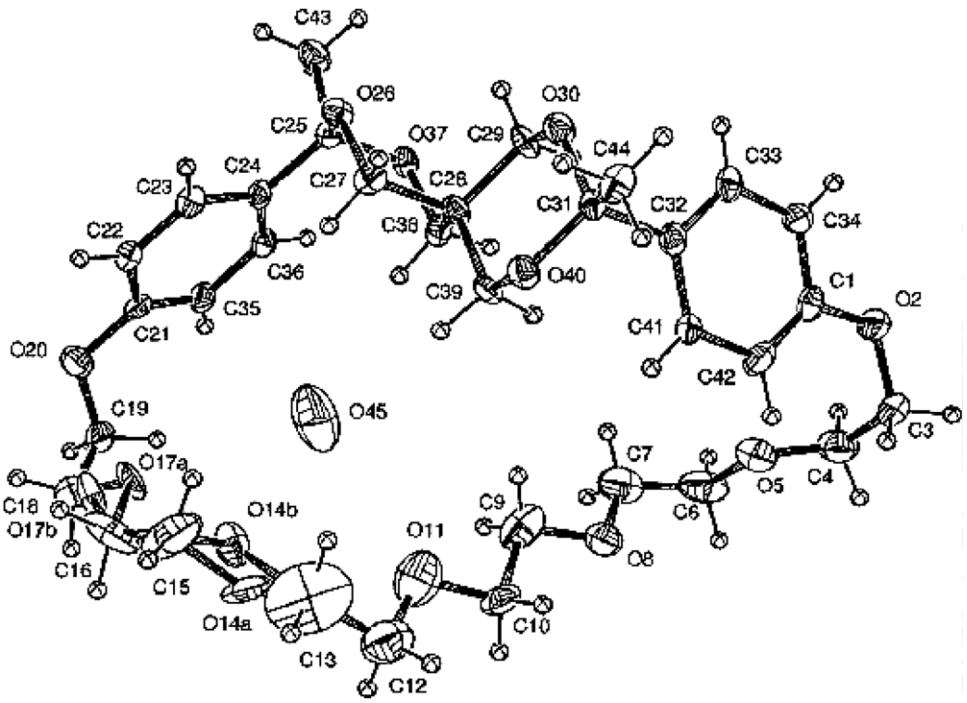


Figure 2. ORTEP diagram of compound **9a**.

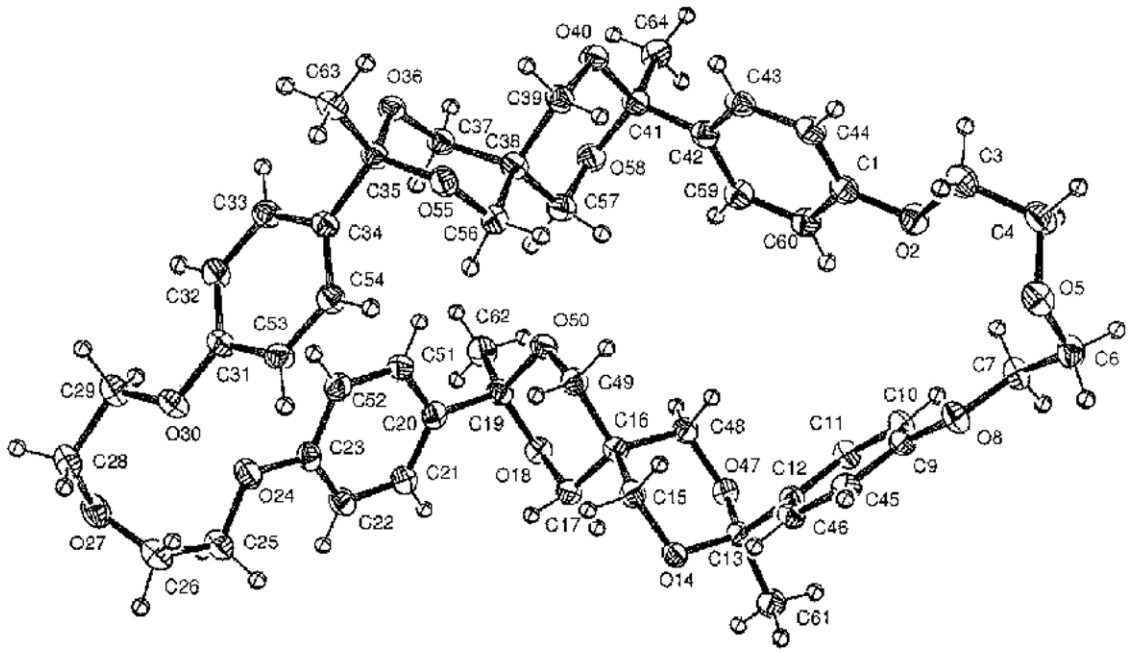


Figure 3. ORTEP diagram of compound **5b**.

Table 2. Values (°) of specific dihedral angles for the rotameric behavior of aromatic rings in solid state for compounds **8a**, **9a** and **5b**

Compound	Dihedral angles	Values	Rotamers[a]
8a	$C^{18}C^{19}C^{20}C^{21}C^{32}C^{33}/C^{21}C^{22}C^{40}$	82.4(4)	*orthogonal*
	$C^{1}C^{29}C^{30}C^{31}C^{38}C^{39}/C^{28}C^{29}C^{41}$	80.4(4)	*orthogonal*
9a	$C^{21}C^{22}C^{23}C^{24}C^{35}C^{36}/C^{24}C^{25}C^{43}$	86.7(8)	*orthogonal*
	$C^{1}C^{32}C^{33}C^{34}C^{41}C^{42}/C^{31}C^{32}C^{44}$	88.5(7)	*orthogonal*
5b	$C^{31}C^{32}C^{33}C^{34}C^{53}C^{54}/C^{34}C^{35}C^{63}$	81.5(1)	*orthogonal*
	$C^{1}C^{42}C^{43}C^{44}C^{59}C^{60}/C^{41}C^{42}C^{64}$	81.3(1)	*orthogonal*
	$C^{9}C^{10}C^{11}C^{12}C^{45}C^{46}/C^{12}C^{13}C^{61}$	80.9(4)	*orthogonal*
	$C^{20}C^{21}C^{22}C^{23}C^{51}C^{52}/C^{19}C^{20}C^{62}$	80.7(5)	*orthogonal*

[a] Values of the dihedral angles close to 0° correspond to the bisectional rotamers and values close to 90° correspond to orthogonal rotamers.

hydrogen bonds (the positions of the hydrogen atoms of the water could not be determined with precision).

The investigated crystal of compound **5b** belongs to the like isomer (the ORTEP diagram represents the PP isomer). The crystal cell is centrosymmetric and the compound is a racemate.

The aromatic rings (**5b**) exhibit a peculiar arrangement close to the T-structure (edge-to-face)[32] suggesting important π-stacking interactions. The dihedral angles formed by the involved aromatic rings are close to 90° ($C^{20}C^{21}C^{22}C^{23}C^{51}C^{52}/C^{31}C^{32}C^{33}C^{34}C^{53}C^{54}$=81.3° and $C^{9}C^{10}C^{11}C^{12}C^{45}C^{46}/C^{1}C^{42}C^{43}C^{44}C^{59}C^{60}$=78.3°) and the distances from the center of an aromatic ring to the center of the opposite aromatic ring are 5.489 and 5.763 Å, respectively. The values of distances from H^{52} and H^{60} to the centers of the opposite aromatic rings (3.34 and 3.76 Å) support the consideration of significant intramolecular stacking interactions in **5b**. These intramolecular interactions explain the peculiar deformed shape of this macrocycle

2.2. Stuctural aspects in solution

The monomeric macrocycles are obtained as racemic (M or P configuration of the helix belonging to the spirane units), while the higher termes are obtained as mixtures of diastereoisomers. The dimers exhibit like (PP, MM) and unlike (PM) isomers. The components of the mixtures of isomers obtained for the dimers were denoted as D^1 (major) and D^2 (minor) because their assignment to like and unlike structures could not be completed. Two diastereoisomers (both chiral; D^3: MMM, PPP and D^4: MPP, PMM) are possible for the trimer and the tetramer shows four diastereoisomers (D^5: MMMM, PPPP; D^6: MPPP, PMMM; D^7: PPMM and D^8: PMPM), two of them (D^7 and D^8) being achiral. The different size cycles (monomers, dimers and the tetramer **5d**) were isolated as mixtures of stereoisomers.

The diastereoisomers of the majority of the dimers could be discriminated in NMR spectra. The spectra of these compounds exhibit two sets of signals, belonging to the like and unlike isomers. Starting from the relative intensities of the well separated peaks (aromatic protons and methyl groups) the ratios of the two stereoisomers (D^1/D^2) could be calculated for the *para* series (compounds **5**-**9**):**5b** (60/40); **6b** (55/45); **7b** (55/45); **8b** (50/50) and **9b** (55/45). The results prove the obtaining of the two diastereoisomers (like and unlike) in close amounts. The ^{1}H and ^{13}C NMR spectra of tetramer **5d** cannot discriminate the different stereoisomers and exhibit unique sets of signals. The shape of the spectra for the different cycles (from monomers to tetramers) are close and generally show the same type of signals. Despite this similarity of the ^{1}H NMR spectra the parts of the spectra of monomers belonging to the protons of the chain display a peculiar pattern. The magnetic anisotropy of the phenylene groups (exhibiting a limitation of their rotation in monomers) and the peculiar orientation of the chain determine significantly different magnetic environments for the protons of the marginal ethyleneoxyde groups (connected to the aromatic rings) and the recording for these protons of four different signals (doublet of doublets of doublets). The diastereotopicity for the α protons ($\Delta\delta$=0.15–0.18 ppm) is higher than the diastereotopicity for the β protons ($\Delta\delta$<0.10 ppm). The ^{1}H NMR spectra of the dimers and of the tetramer **5d** exhibit for the same types of protons only two signals, both α and β protons give (*pseudo*)triplets.

In order to assess the complexing abilities of the new macrocycles (for the cations of the first group) an ESI-MS study was developed with compounds **8a**, **9a** and **5b**-**9b**. The samples were prepared by mixing in volume ratios of 2/1, 1/1 and 1/2 the solution of macrocycle (10^{-6} M) with the solution containing equimolecular amounts (10^{-6} mol/l) of LiI, NaI, KI, RbI and CsI. The experiments were carried out at several cone voltages (17, 20, 25, 38 and 72 V). In all cases a high preference for the complexes with Na^+ (**8a**, **9a**, **5b** and **6b**) or K^+ (**7b**-**9b**) was observed.

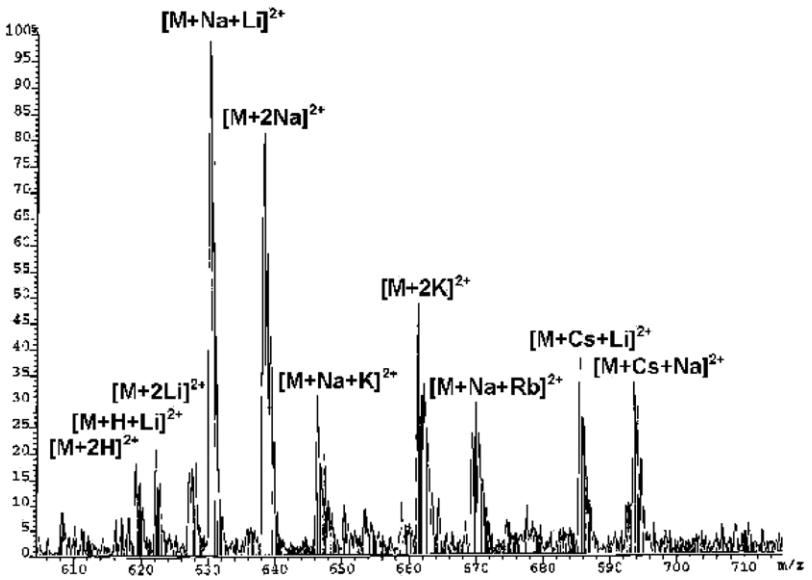


Figure 4. ESI-MS spectrum of compound **9a** obtained at a cone voltage of 17 V and at a ratio macrocycle:salts of 1:2.

Table 3. ESI-MS data (ditopic complexation) of compound **9a** obtained at a cone voltage of 17 V and at a ratio macrocycle:salts of 1:2

Ions	$M+2H^+$	$M+2Li^+$	$M+2Na^+$	$M+2K^+$	$M+Li^++H^+$	$M+Li^++Na^+$	$M+Na^++K^+$	$M+Na^++Rb^+$	$M+Li^++Cs^+$	$M+Na^++Cs^+$
Relative intensities (%)	7.5	7.5	25	20	7.5	50	12.5	12.5	15	15

Even if these results are not spectacular and confirm the high ability of crown-ethers for the complexation with Na^+ and K^+ some of the experiments revealed interesting aspects. The ESI-MS spectra at low cone voltage and at the ratio macrocycle/salts=1/2 showed the capacity of the investigated compounds to coordinate as ditopic ligands (e.g., compound **9a**, Fig. 4, Table 3).

An interesting feature was observed concerning the ability of macrocycles **8a**, **9a** and **5b** to coordinate Cs^+. In an unexpected manner the complexation capacity of the mentioned macrocycles for this cation increases at high cone voltage. As an example, the experiments carried out with compound **8a**, (Fig. 5) showed a dramatic modification of the relative intensity for the $[M+Cs]^+$ peak with the modification of the cone voltage (25 V: 12%; 38 V: 8% and 72 V: 98%). In a similar way at higher cone voltage the complexation ability of **8a** for K^+ (25 V: 32%; 38 V: 12%: and 72 V: 67%). and Rb^+, (25 V: 7%; 38 V: 3%: and 72 V: 31%) is also increased. It can be observed for the complexation of **8a** with all mentioned cations a lowering of the complexation ability in the first step, when the cone voltage is increased from 25 to 38 V (an expected result) and in an unexpected way a dramatic increasing of the complexation ability in the second step when the cone voltage is brought at 78 V. This result is explained by the breaking at high cone voltage of the intramolecular interactions of the macrocycle and the production of larger cavities able to coordinate higher sizes cations (K^+, Rb^+ and Cs^+).

3. Conclusions

The template synthesis of new macrocycles leads to the obtaining in good yields of different size coronands (different lengths of the chain and different terms: from monomers to tetramers). The structural analysis performed on 13 isolated macrocycles (5 monomers, 7 dimers and one tetramer) using high field NMR, mass-spectrometry and X-ray diffractometry investigations reveals the axial orientation of the aromatic substituents, the stacking interactions between the aromatic rings and the inclusion of a molecule of water in the cavity of the monomer macrocycle with six ethyleneoxyde units. The ESI-MS study shows the preference of these macrocycles for the coordination of Na^+ and K^+ but also points out their capacity to coordinate as ditopic ligands.

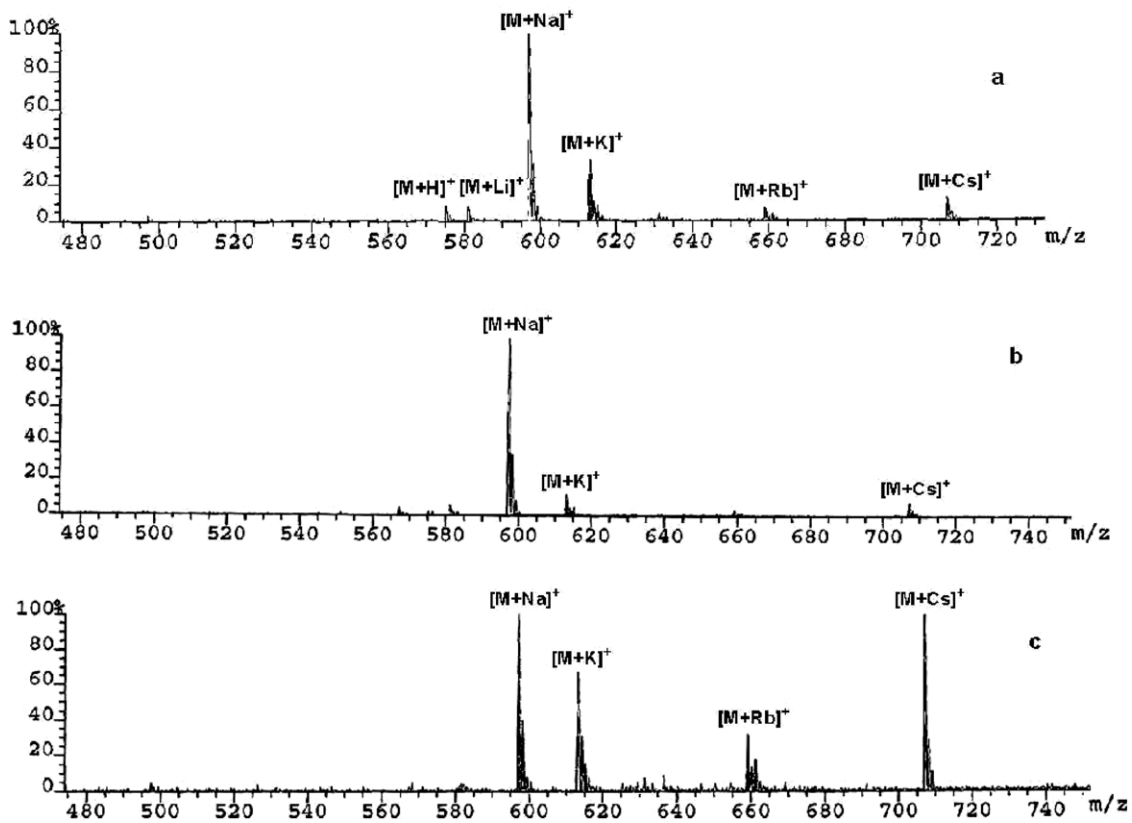


Figure 5. ESI-MS spectra of compound **8a** obtained at a ratio macrocycle:salts of 1:1 and at different cone voltages: 25 V (a), 38 V (b), 72 V (c).

4. Experimental

NMR spectra [^{1}H (600 or 500 MHz), ^{13}C (150 or 125 MHz), COSY, APT, HETCOR (HMBC, HSQC), NOESY or ROESY)] were recorded at rt, in C_6D_6 or $CDCl_3$. Melting points are uncorrected. Microanalyses (C, H) agreed (inside ±0.2%) with calculated data. FAB and MALDI$^+$ spectra were obtained on a JEOL JMS AX-500 spectrometer under usual conditions.

Electrospray ionisation mass spectra (ESI-MS) were recorded on a five-sector mass spectrometer Micromass Autospec-T of EBEBE geometry (where B is a magnetic sector and E is an electric sector) equipped with an atmospheric pressure ionization source and Opus V3.5X data system (Micromass, Manchester, UK). The samples were flow injected at 5 μl/min by means of a syringe pump (Havard Apparatus, model 11) into a needle operating at 8 kV. The voltages of the sampling cone and skimmer lens were varied, while the voltage of the skimmer was fixed at 4 kV. Thus, the resulting potential difference was varied from 17 to 72 V. The temperature of the source was 80 or 40 °C. The nebulization and bath gas were nitrogen (99.995%). Full scan spectra were recorded in positive ions mode over the *m*/*z* range 3000–400 at a scan rate of 5 s/decade. The resolution was 1500. Calibrations were carried out using an equimolar mixture of polypropylene glycols (PPG) 725, 1000, 2000, 3000, 4000 (10^{-5} M).

X-ray crystallographic data for **8a**, **9a** and **5b** are deposited CCDC-194713 (**8a**), 194714 (**9a**) and 194715 (**5b**) at Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk] and they can be obtained free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html.

The HPLC discrimination of different size cycles for **8** and **9** was performed on a C18, Hypersyl (25 cm×4.6 mm, 10 μm) achiral column, using methanol/water (9/1) as elution system at a flow rate of 1.00 ml min^{-1}. Classic UV 2000 (at λ=230 nm) and ESI-MS detections were used.

4.1. General procedure for the synthesis of new compounds 1 and 2

The corresponding ketone (*para* or *meta* acetyloxy-acetophenone, 90 mmol) and 0.2 g of *p*-toluenesulphonic acid were added to a solution of 40 mmol pentaerythritol in 200 ml toluene. The mixture was refluxed and the water resulting from the reaction was removed using a Dean–Stark trap. When the theoretical amount of water was separated, the reaction was cooled at room temperature, and the catalyst was neutralized (under stirring) with excess powdered CH_3COONa (0.4 g). The reaction mixture is washed twice with 100 ml water. The organic layer was dried over Na_2SO_4, then toluene was removed under reduced pressure and the spiro compounds were purified by crystallization from ethanol and dichloromethane (4:1).

4.1.1. 3,9-Dimethyl-3,9-di(*p*-acetyloxyphenyl)-2,4,8,10-tetraoxa spiro[5.5]undecane (1). White crystals (10.16 g, 52%), mp 176–176.5 °C (Found C, 65.93; H, 6.37; $C_{25}H_{28}O_8$ requires: C, 65.78; H, 6.18); δ_H (300 MHz; $CDCl_3$) 1.46 (6H, s, 3-CH_3, 9-CH_3), 2.29 [6H, s, 4′(4″)-O–CO–C*H*$_3$], 3.15 (2H, dd, *J*=11.3, 1.8 Hz, 5-H_{eq}, 7-H_{eq}), 3.24 (2H, d, *J*=11.3 Hz, 5-H_{ax}, 7-H_{ax}), 3.59 (2H, d, *J*=10.9 Hz, 1-H_{ax}, 11-H_{ax}), 4.42 (2H, d, *J*=10.9 Hz, 1-H_{eq}, 11-H_{eq}), 7.09 (4H, d, *J*=8.4 Hz, 3′-H, 5′-H, 3″-H, 5″-H), 7.39 (d, 4H, *J*=8.4 Hz, 2′-H, 6′-H, 2″-H, 6″-H,). δ_C (75 MHz; $CDCl_3$) 21.57 [4′(4″)-O–CO–*C*H$_3$], 32.20 (3-CH_3, 9-CH_3), 32.76 (6-C), 65.03 (5-C, 7-C), 65.36 (1-C, 11-C), 101.19 (3-C, 9-C), 122.25 (3′-C, 5′-C, 3″-C, 5″-C), 128.24 (2′-C, 6′-C, 2″-C, 6″-C), 138.21 (1′-C, 1″-C), 150.65 (4′-C, 4″-C), 169.85 [4′(4″)-O–*C*O–CH$_3$].

4.1.2. 3,9-Dimethyl-3,9-di(*m*-acetyloxyphenyl)-2,4,8,10-tetraox aspiro[5.5]undecane (2). White crystals (9.56 g, 49%), mp 126–127 °C (Found C, 65.49; H, 6.26; $C_{27}H_{36}O_8$ requires: C, 65.78; H, 6.18); δ_H (300 MHz; $CDCl_3$) 1.46 (6H, s, 3-CH_3, 9-CH_3), 2.28 [6H, s, 3′(3″)-O–CO–C*H*$_3$], 3.14 (2H, dd, *J*=11.6, 2.0 Hz, 5-H_{eq}, 7-H_{eq}), 3.22 (2H, d, *J*=11.6 Hz, 5-H_{ax}, 7-H_{ax}), 3.59 (2H, d, *J*=11.6 Hz, 1-H_{ax}, 11-H_{ax}), 4.42 (2H, d, *J*=11.6 Hz, 1-H_{eq}, 11-H_{eq}), 7.02 (2H, dt, *J*=7.9, 1.4 Hz, 4′-H, 4″-H), 7.09 (2H, t, *J*=1.4 Hz, 2′-H, 2″-H); 7.25–7.27 (2H, multiplet, 6′-H, 6″-H); 7.38 (2H, t, *J*=7.9 Hz, 5′-H, 5″-H) δ_C(75 MHz; $CDCl_3$) 21.56 [3′(3″)-O–CO–*C*H$_3$], 32.04 (3-CH_3, 9-CH_3), 32.66 (6-C), 65.10 (5-C, 7-C), 65.43 (1-C, 11-C), 101.03 (3-C, 9-C), 120.43 (4′-C, 4″-C), 121.52 (2′-C, 2″-C), 124.45 (6′-C, 6″-C), 130.23 (5′-C, 5″-C), 142.72 (1′-C, 1″-C), 151.61 (3′-C, 3″-C), 169.82 [3′(3″)-O–*C*O–CH$_3$].

4.2. General procedure for the synthesis of new compounds 3 and 4

A solution (200 ml, 1 M) of LiOH in water was added to the solution (200 ml methanol/THF=1/1) of 40 mmol compounds **1** or **2** to obtain a cloudy mixture that became homogeneous after stirring 12 h at rt. The solvents were removed under reduced pressure and the residue was dissolved in 100 ml of water. The obtained solution was acidulated with oxalic acid till pH 8 and then extracted with 2×200 ml diethyl ether. The organic layers were dried over $MgSO_4$. The ether was removed under reduced pressure and the pure compounds **3** and **4** were obtained by crystallization from chloroform.

4.2.1. 3,9-Dimethyl-3,9-di(*p*-hydoxyphenyl)-2,4,8,10-tetraoxa-spiro[5.5]undecane (3). White crystals (7.68 g, 95%), mp 226–227 °C (Found C, 67.54; H, 6.69; $C_{21}H_{24}O_6$ requires: C, 67.73; H, 6.50); δ_H (300 MHz; C_3D_6O) 1.38 (6H, s, 3-CH_3, 9-CH_3), 3.17 (2H, dd, *J*=11.6, 2.2 Hz, 5-H_{eq}, 7-H_{eq}), 3.27 (2H, d, *J*=11.6 Hz, 5-H_{ax}, 7-H_{ax}), 3.59 (2H, d, *J*=11.3 Hz, 1-H_{ax}, 11-H_{ax}), 4.31 (2H, d, *J*=11.3 Hz, 1-H_{eq}, 11-H_{eq}), 6.85 (4H, d, *J*=8.6 Hz, 3′-H, 5′-H, 3″-H, 5″-H), 7.18 (4H, d, *J*=8.6 Hz, 2′-H, 6′-H, 2″-H, 6″-H), 8.38 [2H, s, 4′(4″)-OH] δ_C (75 MHz; C_3D_6O) 32.72 (3-CH_3, 9-CH_3), 33.24 (6-C), 65.50 (5-C, 7-C), 65.80 (1-C, 11-C), 101.93 (3-C, 9-C), 116.68 (3′-C, 5′-C, 3″-C, 5″-C), 129.09 (2′-C, 6′-C, 2″-C, 6″-C), 132.44 (1′-C, 1″-C), 158.23 (4′-C, 4″-C).

4.2.2. 3,9-Dimethyl-3,9-di(*m*-hydoxyphenyl)-2,4,8,10-tetraoxa-spiro[5.5]undecane (4). White crystals (7.52 g, 93%), mp 186–187 °C (Found C, 67.92; H, 6.65; $C_{23}H_{32}O_6$ requires: C, 67.73; H, 6.50); δ_H (300 MHz; CD_3OD) 1.32

(6H, s, 3-CH_3, 9-CH_3), 3.04 (2H, dd, J=11.8, 2.4 Hz, 5-H_{eq}, 7-H_{eq}), 3.21 (2H, d, J=11.8 Hz, 5-H_{ax}, 7-H_{ax}), 3.55 (2H, d, J=11.6 Hz, 1-H_{ax}, 11-H_{ax}), 4.27 (2H, dd, J=11.6, 2.4 Hz, 1-H_{eq}, 11-H_{eq}), 6.62 (2H, dt, J=7.9, 1.4 Hz, 4′-H, 4″-H), 6.71–6.75 (4H, overlapped peaks, 2′-H, 6′-H, 2″-H, 6″-H); 7.10 (2H, t, J=7.9 Hz, 5′-H, 5″-H), 7.80 [2H, s, 3′(3″)-OH] δ_C (75 MHz; CD_3OD) 32.54 (3-CH_3, 9-CH_3), 33.35 (6-C), 66.18 (5-C, 7-C), 66.54 (1-C, 11-C), 102.62 (3-C, 9-C), 114.87 (2′-C, 2″-C), 116.20 (4′-C, 4″-C), 119.06 (6′-C, 6″-C), 131.31 (5′-C, 5″-C), 143.46 (1′-C, 1″-C), 159.53 (3′-C, 3″-C).

4.3. General procedure for the synthesis of 5-11

Spirane **3** or **4** (5.4 mmol) and 27 mmol Cs_2CO_3 in 0.9 l acetonitrile were refluxed for 2 h. To the obtained suspension, under refluxing solvent, 5.4 mmol of ditosylated polyethyleneglycol dissolved in 0.1 l acetonitrile were added during 4 days using a syringe pump. The reflux of the solvent was continued for one more day. The system was brought to rt and the solid phase removed by filtration. The acetonitrile was evaporated and the crude product was dissolved in 300 ml CH_2Cl_2 and then washed with 2×100 ml solution of KOH 2% and 2×100 ml of water. After drying (Na_2SO_4), the solvent was removed and the crude product was subjected to flash chromatography.

4.3.1. 13,19,35,41-Tetramethyl-2,5,8,14,18,24,27,30,36,40,47,50,55,58-tetradecaoxanonacyclo[40.2.$2^{9,12}$.$2^{13,16}$.$2^{16,19}$.$2^{20,23}$.$2^{31,34}$.$2^{35,38}$.$2^{38,41}$.$2^{1,42}$]hexaconta-9,11,20,22,31,33,42,44(1),45,49,53,59-dodecaene (5b). Colorless solid, mixture of like and unlike isomers, mp 273–275 °C, column chromatography, (ethylacetate/dichloromethane/heptane/methanol=5/20/7.5/0.3; R_f=0.25) 24.0% yield. δ_H (600 MHz; $CDCl_3$) 1.48, 1.50 (s, 12H, 13-CH_3, 19-CH_3, 35-CH_3, 41-CH_3), 3.07 (dd, J=11.7, 2.0 Hz, 4H, 15-H_{eq}, 17-H_{eq}, 37-H_{eq}, 39-H_{eq}), 3.15, 3.17 (d, J=11.7 Hz, 4H, 15-H_{ax}, 17-H_{ax}, 37-H_{ax}, 39-H_{ax}), 3.63, 3.64 (d, J=11.5 Hz, 4H, 48-H_{ax}, 49-H_{ax}, 56-H_{ax}, 57-H_{ax}), 3.89–3.97 (overlapped peaks, 8H, 4-H_2, 6-H_2, 26-H_2, 28-H_2), 4.14–4.21 (overlapped peaks, 8H, 3-H_2, 7-H_2, 25-H_2, 29-H_2), 4.41 (d, J=11.5 Hz, 4H, 48-H_{eq}, 49-H_{eq}, 56-H_{eq}, 57-H_{eq}), 6.91, 6.94 (d, J=8.6 Hz, 8H, 10-H, 22-H, 32-H, 44-H, 45-H, 52-H, 53-H, 60-H), 7.25, 7.28 (d, J=8.6 Hz, 8H, 11-H, 21-H, 33-H, 43-H, 46-H, 51-H, 54-H, 59-H); δ_C (150 MHz; $CDCl_3$) 31.90 (13-CH_3, 19-CH_3, 35-CH_3, 41-CH_3), 32.29, 32.36 (16-C, 38-C), 64.72 (15-C, 17-C, 37-C, 39-C), 65.26 (48-C, 49-C, 56-C, 57-C), 68.19, 68.26 (3-C, 7-C, 25-C, 29-C), 70.30, 70.38 (4-C, 6-C, 26-C, 28-C), 101.09 (13-C, 19-C, 35-C, 41-C), 115.23, 115.29 (10-C, 22-C, 32-C, 44-C, 45-C, 52-C, 53-C, 60-C), 128.07, 128.13 (11-C, 21-C, 33-C, 43-C, 46-C, 51-C, 54-C, 59-C), 132.55, 132.61 (12-C, 20-C, 34-C, 42-C), 158.77 (1-C, 9-C, 23-C, 31-C). MALDI-TOF, m/z=885.3 $[M+H]^+$, 907.5 $[M+Na]^+$, 923.5 $[M+K]^+$. $C_{50}H_{60}O_{14}$ requires: C, 67.86; H, 6.83%; found: C, 67.97; H, 6.76%.

4.3.2. 13,19,35,41,57,63,79,85-Octamethyl-2,5,8,14,18,24,27,30,36,40,46,49,52,58,62,68,71,74,80,84,91,94,99,102,107,110,115,118-octacosaoxaheptadecacyclo[84.2.$2^{9,12}$.$2^{13,16}$.$2^{16,19}$.$2^{20,23}$.$2^{31,34}$.$2^{35,38}$.$2^{38,41}$.$2^{42,45}$.$2^{53,56}$.$2^{57,60}$.$2^{60,63}$.$2^{64,67}$.$2^{75,78}$.$2^{79,82}$.$2^{82,85}$.$2^{1,86}$]cosacenta-9,11,20,22,31,33,42,44,53,55,64,66,75,77,86,88(1),89,95,97,103,105,111,113,119-tetracosaene (5d). Colorless solid, mixture of diastereoisomers, mp 117–119 °C, column chromatography (after the separation of **5b**), (ethylacetate/heptane=5/4; R_f=0.13) 2.0% yield. δ_H (600 MHz; C_6H_6) 1.645, 1.649 (s, 24H, 13-CH_3, 19-CH_3, 35-CH_3, 41-CH_3, 57-CH_3, 63-CH_3, 79-CH_3, 85-CH_3), 2.87 (d, J=11.6 Hz, 8H, 15-H_{eq}, 17-H_{eq}, 37-H_{eq}, 39-H_{eq}, 59-H_{eq}, 61-H_{eq}, 81-H_{eq}, 83-H_{eq}), 3.13 (d, J=11.6 Hz, 8H, 15-H_{ax}, 17-H_{ax}, 37-H_{ax}, 39-H_{ax}, 59-H_{ax}, 61-H_{ax}, 81-H_{ax}, 83-H_{ax}), 3.49–3.51 (overlapped peaks, 16H, 4-H_2, 6-H_2, 26-H_2, 28-H_2, 48-H_2, 50-H_2, 70-H_2, 72-H_2), 3.70 (d, J=11.3 Hz, 8H, 92-H_{ax}, 93-H_{ax}, 100-H_{ax}, 101-H_{ax}, 108-H_{ax}, 109-H_{ax}, 116-H_{ax}, 117-H_{ax}), 3.75–3.77 (overlapped peaks, 16H, 3-H_2, 7-H_2, 25-H_2, 29-H_2, 47-H_2, 51-H_2, 69-H_2, 73-H_2), 4.69 (d, J=11.3 Hz, 8H, 92-H_{eq}, 93-H_{eq}, 100-H_{eq}, 101-H_{eq}, 108-H_{eq}, 109-H_{eq}, 116-H_{eq}, 117-H_{eq}), 6.84 (d, J=8.7 Hz, 16H, 10-H, 22-H, 32-H, 44-H, 54-H, 66-H, 76-H, 88-H, 89-H, 96-H, 97-H, 104-H, 105-H, 112-H, 113-H, 120-H), 7.33 (d, J=8.7 Hz, 16H, 11-H, 21-H, 33-H, 43-H, 55-H, 65-H, 77-H, 87-H, 90-H, 95-H, 98-H, 103-H, 106-H, 111-H, 114-H, 119-H); δ_C (150 MHz; C_6D_6) 32.98 (16-C, 38-C, 60-C, 82-C), 32.99 (13-C, 19-C, 35-C, 41-C, 57-C, 63-C, 79-C, 85-C), 65.34 (15-C, 17-C, 37-C, 39-C, 59-C, 61-C, 81-C, 83-C), 65.93 (92-C, 93-C, 100-C, 101-C, 108-C, 109-C, 116-C, 117-C), 68.28 (3-C, 7-C, 25-C, 29-C, 47-C, 51-C, 69-C, 73-C), 70.56 (4-C, 6-C, 26-C, 28-C, 48-C, 50-C, 70-C, 72-C), 101.85 (13-C, 19-C, 35-C, 41-C, 57-C, 63-C, 79-C, 85-C), 115.74 (10-C, 22-C, 32-C, 44-C, 54-C, 66-C, 76-C, 88-C, 89-C, 96-C, 97-C, 104-C, 105-C, 112-C, 113-C, 120-C), 129.09 (11-C, 21-C, 33-C, 43-C, 55-C, 65-C, 77-C, 87-C, 90-C, 95-C, 98-C, 103-C, 106-C, 111-C, 114-C, 119-C), 133.71 (12-C, 20-C, 34-C, 42-C, 56-C, 64-C, 78-C, 86-C), 159.63 (1-C, 9-C, 23-C, 31-C, 45-C, 53-C, 67-C, 75-C). MALDI-TOF, m/z=1791.0 $[M+Na]^+$, 1808.2 $[M+K]^+$. $C_{100}H_{120}O_{28}$ requires: C, 67.86; H, 6.83%; found: C, 67.93; H, 6.98%.

4.3.3. 16,22,41,47-Tetramethyl-2,5,8,11,17,21,27,30,33,36,42,46,53,56,61,64-hexadecaoxanonacyclo[46.2.2^{12,15}.$2^{16,19}$.$2^{19,22}$.$2^{23,26}$.$2^{37,40}$.$2^{41,44}$.$2^{44,47}$.$2^{1,48}$]hexahexaconta-12,14,23,25,37,39,48,50(1),51,57,59,65-tetradecaene (6b). Colorless solid, mixture of like and unlike isomers, mp 149–150 °C, column chromatography, (ethylacetate/heptane=3/2; R_f=0.24) 34.0% yield. δ_H (600 MHz; $CDCl_3$) 1.47, 1.48 (s, 12H, 16-CH_3, 22-CH_3, 41-CH_3, 47-CH_3), 3.09, 3.12 (dd, J=11.7, 2.2 Hz, 4H, 18-H_{eq}, 20-H_{eq}, 43-H_{eq}, 45-H_{eq}), 3.19, 3.22 (d, J=11.7 Hz, 4H, 18-H_{ax}, 20-H_{ax}, 43-H_{ax}, 45-H_{ax}), 3.57, 3.61 (d, J=11.6 Hz, 4H, 54-H_{ax}, 55-H_{ax}, 62-H_{ax}, 63-H_{ax}), 3.76 (s, 8H, 6-H_2, 7-H_2, 31-H_2, 32-H_2), 3.87–3.89 (overlapped peaks, 8H, 4-H_2, 9-H_2, 29-H_2, 34-H_2], 4.11–4.16 (overlapped peaks, 8H, 3-H_2, 10-H_2, 28-H_2, 35-H_2), 4.40, 4.42 (dd, J=11.6, 2.2 Hz, 4H, 54-H_{eq}, 55-H_{eq}, 62-H_{eq}, 63-H_{eq}), 6.91, 6.92 (d, J=8.8 Hz, 8H, 13-H, 25-H, 38-H, 50-H, 51-H, 58-H, 59-H, 66-H), 7.275, 7.278 (d, J=8.8 Hz, 8H, 14-H, 24-H, 39-H, 49-H, 52-H, 57-H, 60-H, 65-H); δ_C (150 MHz; $CDCl_3$) 31.88, 31.99 (16-CH_3, 22-CH_3, 41-CH_3, 47-CH_3), 32.27, 32.32 (19-C, 44-C), 64.80 (18-C, 20-C, 43-C, 45-C), 65.16 (54-C, 55-C, 62-C, 63-C), 67.68 (3-C, 10-C, 28-C, 35-C), 69.93 (4-C, 9-C, 29-C, 34-C), 71.17 (6-C, 7-C, 31-C, 32-C), 101.09 (16-C, 22-C, 41-C, 47-C), 114.94 (13-C, 25-C, 38-C, 50-C, 51-C, 58-C, 59-C, 66-C), 128.10 (14-C, 24-C, 39-C, 49-C, 52-C, 57-C, 60-C, 65-C), 132.46, 132.50 (15-C, 23-C, 40-C, 48-C),

158.61 (1-C, 12-C, 26-C, 37-C). FAB, m/z=973.5 $[M+H]^+$. $C_{54}H_{68}O_{16}$ requires: C, 66.65; H, 7.04%; found: C, 66.46; H, 7.18%.

4.3.4. 19,25-Dimethyl-2,5,8,11,14,20,24,31,34-nona-oxapentacyclo[24.2.2^{15,18}.2^{19,22}.2^{22,25}. 2^{1,26}]hexatriaconta-15,17,26,28(1),29,35-hexaene (7a). Colorless oil, column chromatography, (chloroform/ethylacetate/heptane/methanol=4/1/5/0.1; R_f=0.28) 6.0% yield. δ_H (500 MHz; C_6D_6) 1.64 (s, 6H, 19-CH_3, 25-CH_3), 2.63 (d, J=11.5 Hz, 2H, 21-H_{eq}, 23-H_{eq}), 3.34 (d, J=11.5 Hz, 2H, 21-H_{ax}, 23-H_{ax}), 3.15–3.37 (overlapped peaks, 12H, 4-H_2, 6-H_2, 7-H_2, 9-H_2 10-H_2, 12-H_2), 3.66 (d, J=11.0 Hz, 2H, 32-H_{ax}, 33-H_{ax}), 3.77 [ddd, J=13.0, 5.5, 3.0 Hz, 2H, 3-H(H′), 13-H(H′)], 3.90 (d, J=11.0 Hz, 2H, 32-H_{eq}, 33-H_{eq}), 3.93 [ddd, J=13.0, 6.5, 3.0 Hz, 2H, 3-H(H'), 13-H(H')], 6.92 (d, J=9.0 Hz, 4H, 16-H, 28-H, 29-H, 36-H), 7.36 (d, J=9.0 Hz, 4H, 17-H, 27-H, 30-H, 35-H); δ_C (125 MHz; C_6D_6) 30.66 (19-CH_3, 25-CH_3), 36.46 (22-C), 64.58 (21-C, 23-C), 65.28 (32-C, 33-C), 68.32 (3-C, 13-C), 70.94, 71.17, 71.42 (4-C, 6-C, 7-C, 9-C, 10-C, 12-C), 101.54 (19-C, 25-C), 116.55 (16-C, 28-C, 29-C, 36-C), 135.02 (18-C, 26-C), 159.70 (1-C, 15-C), MS (EI, 70 eV): m/z=530 $[M]^+$. $C_{29}H_{38}O_9$ requires: C, 65.64; H, 7.22%; found: C, 65.82; H, 7.03%.

4.3.5. 19,25,47,53-Tetramethyl-2,5,8,11,14,20,24,30,33,36,39,42,48,52,59,62,67,70-octadecaoxanonacyclo-[52.2.2^{15,18}.2^{19,22}.2^{22,25}.2^{26,29}.2^{43,46}.2^{47,50}.2^{50,53}.2^{1,54}]doheptaconta-15,17,26,28,43,45,54,56(1),57,63,65,71-dodecaene (7b). Colorless solid, mixture of like and unlike isomers, mp 175–177 °C, column chromatography, (chloroform/ethylacetate/heptane/methanol=4/1/5/0.1; R_f=0.16) 18.0% yield. δ_H (600 MHz; C_6D_6) 1.63, 1.64 (s, 12H, 19-CH_3, 25-CH_3, 47-CH_3, 53-CH_3), 2.92–2.94 (overlapped peaks, 4H, 21-H_{eq}, 23-H_{eq}, 49-H_{eq}, 51-H_{eq}), 3.17, 3.18 (d, J=12.0 Hz, 4H, 21-H_{ax}, 23-H_{ax}, 49-H_{ax}, 51-H_{ax}), 3.45 (s, 16H, 6-H_2, 7-H_2, 9-H_2, 10-H_2, 34-H_2, 35-H_2, 37-H_2, 38-H_2), 3.55–3.58 (overlapped peaks, 8H, 4-H_2, 12-H_2, 32-H_2, 40-H_2], 3.70, 3.71 (d, J=11.4 Hz, 4H, 60-H_{ax}, 61-H_{ax}, 68-H_{ax}, 69-H_{ax}), 3.80–3.81 (overlapped peaks, 8H, 3-H_2, 13-H_2, 31-H_2, 41-H_2), 4.68, 4.70 (d, J=11.4 Hz, 4H, 60-H_{eq}, 61-H_{eq}, 68-H_{eq}, 69-H_{eq}), 6.87 (d, J=8.0 Hz, 8H, 16-H, 28-H, 44-H, 56-H, 57-H, 64-H, 65-H, 72-H), 7.34, 7.35 (d, J=8.0 Hz, 8H, 17-H, 27-H, 45-H, 55-H, 58-H, 63-H, 66-H, 71-H); δ_C (75 MHz; C_6D_6) 32.99 (22-C, 50-C), 33.05 (19-CH_3, 25-CH_3, 47-CH_3, 53-CH_3), 65.37 (21-C, 23-C, 49-C, 51-C), 65.89 (60-C, 61-C, 68-C, 69-C), 68.29 (3-C, 13-C, 31-C, 41-C), 70.49 (4-C, 12-C, 32-C, 40-C), 71.71, 71.76, 71.79 (6-C, 7-C, 9-C, 10-C, 34-C, 35-C, 37-C, 38-C), 101.85 (19-C, 25-C, 47-C, 53-C), 115.75 (16-C, 28-C, 44-C, 56-C, 57-C, 64-C, 65-C, 72-C), 133.58 (18-C, 26-C, 46-C, 54-C) 159.68 (1-C, 15-C, 29-C, 43-C); MALDI-TOF, m/z=1061.2 $[M+H]^+$, 1083.7 $[M+Na]^+$, 1100.2 $[M+K]^+$. $C_{58}H_{76}O_{18}$ requires: C, 65.64; H, 7.22%; found: C, 65.49; H, 7.08%.

4.3.6. 22,28-Dimethyl-2,5,8,11,14,17,23,27,34,37-decaoxa-pentacyclo[27.2.2^{18,21}.2^{22,25}.2^{25,28}.2^{1,29}]nonatriaconta-18,20,29,31(1),32,38-hexaene (8a). Colorless solid, mp 118 °C, column chromatography, (ethylacetate/dichloromethane/petroleum ether/methanol=10/5/3/0.2; R_f=0.40) 20.0% yield. δ_H (600 MHz; C_6D_6) 1.65 (s, 6H, 22-CH_3, 28-CH_3), 2.77 (d, J=11.7 Hz, 2H, 24-H_{eq}, 26-H_{eq}), 3.13 (d, J=11.7 Hz, 2H, 24-H_{ax}, 26-H_{ax}), 3.15–3.26 (overlapped peaks, 8H, 6-H_2, 7-H_2, 12-H_2, 13-H_2), 3.26 [ddd, J=13.9, 5.5, 2.6 Hz, 2H, 4-H(H′), 15-H(H′)], 3.31 (s, 4H, 9-H_2, 10-H_2), 3.33 [ddd, J=13.9, 6.6, 2.7 Hz, 2H, 4-H(H'), 15-H(H')], 3.78 [ddd, J=12.4, 5.5, 2.7 Hz, 2H, 3-H(H′), 16-H(H')], 3.89 (d, J=11.2 Hz, 2H, 35-H_{ax}, 36-H_{ax}), 3.96 [ddd, J=12.4, 6.6, 2.6 Hz, 2H, 3-H(H'), 16-H(H')], 4.00 (d, J=11.2 Hz, 2H, 35-H_{eq}, 36-H_{eq}), 6.97 (d, J=8.6 Hz, 4H, 19-H, 31-H, 32-H, 39-H), 7.35 (d, J=8.6 Hz, 4H, 20-H, 30-H, 33-H, 38-H); δ_C (150 MHz; C_6D_6) 31.01 (22-CH_3, 28-CH_3), 34.91 (25-C), 64.54 (24-C, 26-C), 65.88 (35-C, 36-C), 68.44 (3-C, 16-C), 71.13 (9-C, 10-C), 71.23, 71.27 (6-C, 7-C, 12-C, 13-C), 71.49 (4-C, 15-C), 101.64 (22-C, 28-C), 116.51 (19-C, 31-C, 32-C, 39-C), 128.61 (20-C, 30-C, 33-C, 38-C), 134.36 (21-C, 29-C), 159.74 (1-C, 18-C); MS (CI, 150 eV): m/z=575 $[M+H]^+$. $C_{31}H_{42}O_{10}$ requires: C, 64.79; H, 7.37%; found: C, 64.66; H, 7.51%.

4.3.7. 22,28,53,59-Tetramethyl-2,5,8,11,14,17,23,27,33,36,39,42,45,48,54,58,65,68,73,76-cosaoxanonacyclo-[58.2.2^{18,21}.2^{22,25}.2^{25,28}.2^{29,32}.2^{49,52}.2^{53,56}.2^{56,59}.2^{1,60}]octaheptaconta-18,20,29,31,49,51,60,62(1),63,69,71,77-dodecaene (8b). Colorless solid, mixture of like and unlike isomers, mp 148–149 °C, column chromatography, (ethylacetate/dichloromethane/petroleum ether/methanol=10/5/3/0.2; R_f=0.10) 22.0% yield. δ_H (600 MHz; C_6D_6) 1.64, 1.65 (s, 12H, 22-CH_3, 28-CH_3, 53-CH_3, 59-CH_3), 2.91 (d, J=11.4 Hz, 4H, 24-H_{eq}, 26-H_{eq}, 55-H_{eq}, 57-H_{eq}), 3.172, 3.178 (d, J=11.4 Hz, 4H, 24-H_{ax}, 26-H_{ax}, 55-H_{ax}, 57-H_{ax}), 3.452, 3.454 (s, 24H, 6-H_2, 7-H_2, 9-H_2, 10-H_2, 12-H_2, 13-H_2, 37-H_2, 38-H_2, 40-H_2, 41-H_2, 43-H_2, 44-H_2), 3.54–3.57 (overlapped peaks, 8H, 4-H_2, 15-H_2, 35-H_2, 46-H_2), 3.71 (d, J=11.4 Hz, 4H, 66-H_{ax}, 67-H_{ax}, 74-H_{ax}, 75-H_{ax}), 3.801–3.816 (overlapped peaks, 8H, 3-H_2, 16-H_2, 34-H_2, 47-H_2), 4.71 (d, J=11.4 Hz, 4H, 66-H_{eq}, 67-H_{eq}, 74-H_{eq}, 75-H_{eq}), 6.87, 6.88 (d, J=8.6 Hz, 8H, 19-H, 31-H, 50-H, 62-H, 63-H, 70-H, 71-H, 78-H), 7.34, 7.35 (d, J=8.6 Hz, 8H, 20-H, 30-H, 51-H, 61-H, 64-H, 69-H, 72-H, 77-H); δ_C (75 MHz; C_6D_6) 32.99 (22-CH_3, 28-CH_3, 53-CH_3, 59-CH_3), 33.02 (25-C, 56-C), 65.37 (24-C, 26-C, 55-C, 57-C), 65.91 (66-C, 67-C, 74-C, 75-C), 68.30 (3-C, 16-C, 34-C, 47-C), 70.48 (9-C, 10-C, 40-C, 41-C), 71.67 (6-C, 7-C, 12-C, 13-C, 37-C, 38-C, 43-C, 44-C), 71.77 (4-C, 15-C, 35-C, 46-C), 101.86 (22-C, 28-C, 53-C, 59-C), 115.74 (19-C, 31-C, 50-C, 62-C, 63-C, 70-C, 71-C, 78-C), 133.58 (21-C, 29-C, 52-C, 60-C), 159.69 (1-C, 18-C, 32-C, 49-C); MALDI-TOF, m/z=1171.1 $[M+Na]^+$, 1187.0 $[M+K]^+$. $C_{62}H_{84}O_{20}$ requires: C, 64.79; H, 7.37%; found: C, 64.68; H, 7.21%.

4.3.8. 25,31-Dimethyl-2,5,8,11,14,17,20,26,30,37,40-undeca-oxapentacyclo[30.2.2^{21,24}.2^{25,28}.2^{28,31}.2^{1,32}]dotetraconta-21,23,32,34(1),35,41-hexaene (9a). Colorless solid, mp 97–98 °C, column chromatography, (dichloromethane/methanol=32/1; R_f=0.33) 17.0% yield. δ_H (600 MHz; C_6D_6) 1.66 (s, 6H, 25-CH_3, 31-CH_3), 3.01 (d, J=11.7 Hz, 2H, 27-H_{eq}, 29-H_{eq}), 3.07 (d, J=11.7 Hz, 2H, 27-H_{ax}, 29-H_{ax}), 3.21–3.39 (overlapped peaks, 20H, 4-H_2, 6-H_2, 7-H_2, 9-H_2, 10-H_2, 12-H_2, 13-H_2, 15-H_2, 16-H_2, 18-H_2), 3.81 [ddd, J=12.3, 5.5, 2.6 Hz, 2H, 3-H(H′), 19-H(H′)], 3.85 (d, J=11.4 Hz, 2H, 38-H_{ax}, 39-H_{ax}), 3.95 [ddd, J=12.3, 6.6, 2.4 Hz, 2H, 3-H(H'), 19-H(H')], 4.31 (d, J=11.4 Hz, 2H, 38-H_{eq}, 39-H_{eq}), 7.01 (d, J=8.7 Hz, 4H, 22-H, 34-H, 35-H, 42-H), 7.36 (d, J=8.7 Hz, 4H, 23-H, 33-H,

36-H, 41-H); δ_C (150 MHz; C_6D_6) 31.64 (25-CH_3, 31-CH_3), 33.89 (28-C), 64.89 (27-C, 29-C), 66.10 (38-C, 39-C), 68.62 (3-C, 19-C), 71.28, 71.33, 71.36, 71.43, 71.54 (4-C, 6-C, 7-C, 9-C, 10-C, 12-C, 13-C, 15-C, 16-C, 18-C), 101.74 (25-C, 31-C), 116.58 (22-C, 34-C, 35-C, 42-C), 128.91 (23-C, 33-C, 36-C, 41-C), 133.96 (24-C, 32-C), 159.82 (1-C, 21-C); MS (CI, 150 eV): m/z=619 $[M+H]^+$. $C_{33}H_{46}O_{11}$ requires: C, 64.06; H, 7.49%; found: C, 63.88; H, 7.66%.

4.3.9. 25,31,59,65-Tetramethyl-2,5,8,11,14,17,20,26,30,36,39,42,45,48,51,54,60,64,71,74,79,82-docosaoxa-nonacyclo[64.2.2^{21,24}.2^{25,28}.2^{28,31}.2^{32,35}.2^{55,58}.2^{59,62}.2^{62,65}.2^{1,66}]-tetraoctaconta-21,23,32,34,55,57,66,68(1),69,75,77,83-dodecaene (9b). Colorless oil, mixture of like and unlike isomers, column chromatography, (dichloromethane/methanol=32/1; R_f=0.22) 15.0% yield. δ_H (600 MHz; $CDCl_3$) 1.46, 1.47 (s, 12H, 25-CH_3, 31-CH_3, 59-CH_3, 65-CH_3), 3.11 (d, J=11.4 Hz, 4H, 27-H_{eq}, 29-H_{eq}, 61-H_{eq}, 63-H_{eq}), 3.22 (d, J=11.4 Hz, 4H, 27-H_{ax}, 29-H_{ax}, 61-H_{ax}, 63-H_{ax}), 3.60 (d, J=11.4 Hz, 4H, 72-H_{ax}, 73-H_{ax}, 80-H_{ax}, 81-H_{ax}), 3.65–3.73 (overlapped peaks, 32H, 6-H_2, 7-H_2, 9-H_2, 10-H_2, 12-H_2, 13-H_2, 15-H_2, 16-H_2, 40-H_2, 41-H_2, 43-H_2, 44-H_2, 46-H_2, 47-H_2, 49-H_2, 50-H_2), 3.85–3.86 (overlapped peaks, 8H, 4-H_2, 18-H_2, 38-H_2, 52-H_2), 4.12–4.14 (overlapped peaks, 8H, 3-H_2, 19-H_2, 37-H_2, 53-H_2), 4.41 (d, J=11.4 Hz, 4H, 72-H_{eq}, 73-H_{eq}, 80-H_{eq}, 81-H_{eq}), 6.91, 6.92 (d, J=8.8 Hz, 8H, 22-H, 34-H, 56-H, 68-H, 69-H, 76-H, 77-H, 84-H), 7.29, 7.30 (d, J=8.8 Hz, 8H, 23-H, 33-H, 57-H, 67-H, 70-H, 75-H, 78-H, 83-H); δ_C (150 MHz; $CDCl_3$) 32.01 (25-CH_3, 31-CH_3, 59-CH_3, 65-CH_3), 32.39 (28-C, 62-C), 64.83 (27-C, 29-C, 61-C, 63-C), 65.15 (72-C, 73-C, 80-C, 81-C), 67.65 (3-C, 19-C, 37-C, 53-C), 69.92 (4-C, 18-C, 38-C, 52-C), 70.77, 70.84, 70.90, 71.09 (6-C, 7-C, 9-C, 10-C, 12-C, 13-C, 15-C, 16-C, 40-C, 41-C, 43-C, 44-C, 46-C, 47-C, 49-C, 50-C), 101.11 (25-C, 31-C, 59-C, 65-C), 114.93 (22-C, 34-C, 56-C, 68-C, 69-C, 76-C, 77-C, 84-C), 128.16 (23-C, 33-C, 57-C, 67-C, 70-C, 75-C, 78-C, 83-C), 132.50 (24-C, 32-C, 58-C, 66-C), 158.61 (1-C, 21-C, 35-C, 55-C); MALDI-TOF, m/z=1237.4 $[M+H]^+$, 1259.6 $[M+Na]^+$, 1275.7 $[M+K]^+$. $C_{66}H_{92}O_{22}$ requires: C, 64.06; H, 7.49%; found: C, 64.21; H, 7.54%.

4.3.10. 14,20,38,44-Tetramethyl-2,5,8,15,19,26,29,32,39,43,50,53,56,59-tetradecaoxanonacyclo[43.3.2^{14,17}.2^{17,20}.2^{38,41}.2^{41,44}.1^{1,45}.1^{9,13}.1^{21,25}.1^{33,37}]hexaconta-1(60),9,11,13(49),21,23,25(54),33,35,37(55),45,47-dodecaene (10b). Colorless solid, mixture of like and unlike isomers, mp 126–128 °C, column chromatography, (ethylacetate/dichloromethane/heptane=1/4/2; R_f=0.13) 27.0% yield δ_H (500 MHz; $CDCl_3$) 1.45 (s, 12H, 14-CH_3, 20-CH_3, 38-CH_3, 44-CH_3), 3.05 (dd, J=12.0, 2.0 Hz, 4H, 16-H_{eq}, 18-H_{eq}, 40-H_{eq}, 42-H_{eq}), 3.19 (d, J=12.0 Hz, 4H, 16-H_{ax}, 18-H_{ax}, 40-H_{ax}, 42-H_{ax}), 3.62 (d, J=11.5 Hz, 4H, 51-H_{ax}, 52-H_{ax}, 57-H_{ax}, 58-H_{ax}), 3.90–3.93 (overlapped peaks, 8H, 4-H_2, 6-H_2, 28-H_2, 30-H_2), 4.12–4.14 (t, J=4.8 Hz, 8H, 3-H_2, 7-H_2, 27-H_2, 31-H_2], 4.41 (dd, J=11.5, 2.0 Hz, 4H, 51-H_{eq}, 52-H_{eq}, 57-H_{eq}, 58-H_{eq}), 6.83, 6.84 [dt (overlapped ddd), J=8.0, 2.0 Hz, 4H, 10-H, 24-H, 34-H, 48-H], 6.91–6.92 (overlapped peaks, 4H, 49-H, 54-H, 55-H, 60-H); 7.00 [dt (overlapped ddd), J=8.0, 2.0 Hz, 4H, 12-H, 22-H, 36-H, 46-H]; 7.28 (t, J 8.0 Hz, 4H, 11-H, 23-H, 35-H, 47-H); δ_C (125 MHz; $CDCl_3$) 32.00 (14-CH_3, 20-CH_3, 38-CH_3, 44-CH_3), 32.24 (17-C, 41-C), 65.02 (16-C, 18-C, 40-C, 42-C), 65.34 (51-C, 52-C, 57-C, 58-C), 67.71 (3-C, 7-C, 27-C, 31-C), 70.27 (4-C, 6-C, 28-C, 30-C), 101.15 (14-C, 20-C, 38-C, 44-C), 112.95 (49-C, 54-C, 55-C, 60-C), 114.21 (10-C, 24-C, 34-C, 48-C), 119.49 (12-C, 22-C, 36-C, 46-C), 130.07 (11-C, 23-C, 35-C, 47-C), 142.24 (13-C, 21-C, 37-C, 45-C), 159.54 (9-C, 25-C, 33-C, 1-C); MALDI-TOF, m/z=885.0 (M+1), 907.5 $[M+Na]^+$, 923.4 $[M+K]^+$. $C_{50}H_{60}O_{14}$ requires: C, 67.86; H, 6.83%; found: C, 67.92; H, 6.90%.

4.3.11. 17,23-Dimethyl-2,5,8,11,18,22,29,32-octaoxa-penta-cyclo[22.3.2^{17,20}.2^{20,23}.1^{1,24}.1^{12,16}]tritriaconta-1(33),12,14,16(28),24,26-hexaene (11a). Colorless oil, column chromatography, (ethylacetate/heptane=2/3; R_f=0.35) 15.0% yield. δ_H (600 MHz; C_6D_6) 1.63 (s, 6H, 17-CH_3, 23-CH_3), 3.11 (d, J=11.5 Hz, 2H, 19-H_{eq}, 21-H_{eq}), 3.31–3.38 [overlapped peaks, 6H, 4-H(H′), 9-H(H′)], 6-H_2, 7-H_2), 3.44 [ddd, J=10.8, 6.0, 4.8 Hz, 2H, 4-H(H'), 9-H(H')], 3.64 (d, J=11.5 Hz, 2H, 19-H_{ax}, 21-H_{ax}), 3.68 (d, J=11.3 Hz, 2H, 30-H_{ax}, 31-H_{ax}), 3.87 (d, J=11.3 Hz, 2H, 30-H_{eq}, 31-H_{eq}), 3.95 [ddd, J=12.0, 5.4, 4.8 Hz, 2H, 3-H(H′), 10-H(H′)], 4.01 [ddd, J=12.0, 6.0, 4.8 Hz, 2H, 3-H(H'), 10-H(H')], 6.91 (ddd, J=8.0, 2.4, 1.2 Hz, 2H, 13-H, 27-H), 7.03 [dt (overlapped ddd), J=8.0, 1.5, 1.2 Hz, 2H, 15-H, 25-H]; 7.10 [t (overlapped dd), J=8.0 Hz, 2H, 14-H, 26-H]; 7.58 (dd, J=2.4, 1.2 Hz, 2H, 28-H, 33-H]; δ_C (150 MHz; C_6D_6) 28.48 (17-CH_3, 23-CH_3), 35.15 (20-C), 65.03 (19-C, 21-C), 65.95 (30-C, 31-C), 68.47 (3-C, 10-C), 70.70 (4-C, 9-C), 71.10 (6-C, 7-C), 101.31 (17-C, 23-C), 113.66 (28-C, 33-C), 117.78 (13-C, 27-C), 119.89 (15-C, 25-C), 130.39 (14-C, 26-C), 144.37 (16-C, 24-C), 160.36 (1-C, 12-C); MS (EI, 70 eV): m/z=486 $[M]^+$.$C_{27}H_{34}O_8$ requires: C, 66.65; H, 7.04%; found: C, 66.59; H, 7.18%.

4.3.12. 17,23,44,50-Tetramethyl-2,5,8,11,18,22,29,32,35,38,45,49,56,59,62,65-hexadecaoxanona cyclo[49.3.2^{17,20}.2^{20,23}.2^{44,47}.2^{47,50}.1^{1,51}.1^{12,16}.1^{24,28}.1^{39,43}]hexa hexaconta-1(66),12,14,16(55),24,26,28(60),39,41,43(61),51,53-dodecaene (11b). Colorless solid, mixture of like and unlike isomers, mp 139–140 °C, column chromatography, (ethylacetate/heptane=2/3; R_f=0.11) 17.0% yield. δ_H (500 MHz; $CDCl_3$) 1.44, 1.45 (s, 12H, 17-CH_3, 23-CH_3, 44-CH_3, 50-CH_3), 3.07 (d, J=11.5 Hz, 4H, 19-H_{eq}, 21-H_{eq}, 46-H_{eq}, 48-H_{eq}), 3.22 (d, J=11.5 Hz, 4H, 19-H_{ax}, 21-H_{ax}, 46-H_{ax}, 48-H_{ax}), 3.60 (d, J=11.5 Hz, 4H, 57-H_{ax}, 58-H_{ax}, 63-H_{ax}, 64-H_{ax}), 3.74 (s, 8H, 6-H_2, 7-H_2, 33-H_2, 34-H_2), 3.84–3.86 (overlapped peaks, 8H, 4-H_2, 9-H_2, 31-H_2, 36-H_2), 4.08–4.11 (overlapped peaks, 8H, 3-H_2, 10-H_2, 30-H_2, 37-H_2), 4.41 (d, J=11.5 Hz, 4H, 57-H_{eq}, 58-H_{eq}, 63-H_{eq}, 64-H_{eq}), 6.82, 6.83 [dt (overlapped ddd), 4H, 13-H, 27-H, 40-H, 54-H), 6.93–6.99 (overlapped peaks, 8H, 15-H, 25-H, 42-H, 52-H, 55-H, 60-H, 61-H, 66-H), 7.25 (t, J=7.5 Hz, 4H, 14-H, 26-H, 41-H, 53-H); δ_C (125 MHz; $CDCl_3$) 31.90 (17-CH_3, 23-CH_3, 44-CH_3, 50-CH_3), 32.27 (20-C, 47-C), 65.00 (19-C, 21-C, 46-C, 48-C), 65.31 (57-C, 58-C, 63-C, 64-C), 67.67 (3-C, 10-C, 30-C, 37-C), 70.04 (4-C, 9-C, 31-C, 36-C), 71.11, 71.19 (6-C, 7-C, 33-C, 34-C), 101.13 (17-C, 23-C, 44-C, 50-C), 113.13 (55C, 60-C, 61-C, 66-C), 114.18 (13-C, 27-C, 40-C, 54-C), 119.37 (15-C, 25-C, 42-C, 52-C), 130.03 (14-C, 26-C, 41-C, 53-C), 142.25 (16-C, 24-C, 43-C, 51-C), 159.57 (1-C, 12-C, 28-C, 39-C); MALDI-TOF, m/z=995.2 $[M+Na]^+$, 1011.2 $[M+K]^+$.

$C_{54}H_{68}O_{16}$ requires: C, 66.65; H, 7.04%; found: C, 66.83; H, 6.92%.

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Theoretical investigations on $R(O)_nS-NO$ ($n=0,1,2$) systems☆

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Abstract—In the current article we report the ab initio study on the stability of *S*-Nitrosothiols (MeSNO, **1**) and their oxidised derivatives (MeS(O)NO, **2**) and ($MeS(O)_2NO$, **3**). The bond length, bond order, rotational barrier and bond dissociation energy have been calculated and compared with that of sulfenamide ($HS-NH_2$) and its oxidised derivatives sulfinamide ($H(O)S-NH_2$) and sulfonamide ($H(O)_2S-NH_2$). The S–N bond dissociation energy in the oxidised state is very small compared to parent RSNO indicating the weakness of sigma bond. NBO analysis suggests that the negative hyperconjugative interactions are very strong in *S*-nitrosothiols and their oxidised derivatives, which weaken the sigma bond and facilitate the release of nitric oxide.

1. Introduction

In the past ten years, remarkable progress has been made in the chemistry and biology of nitric oxide (NO) owing to the fact that nitric oxide plays an important role in the pathophysiology of human beings. Deficiency of nitric oxide leads to pathological and physiological complications in vivo. When the body cannot generate enough nitric oxide for normal physiological functions, exogenous supply of nitric oxide into bloodstream in a sustained and controlled manner is essential. Many novel nitric oxide donors such as *S*-Nitrosothiols,[1] diazonium diolates,[2] mesoionic oxatriazole,[3] hybrid NSAID–NO donor drugs like NO-paracetamol, NO-aspirin and NO-flurbiprofen,[4] etc. have been found to be useful in the treatment of various clinical conditions, particularly coronary artery diseases such as vasodilatation and inhibition of platelet aggregation. As a unique category of such NO-carrying vehicles, *S*-Nitrosothiols (RSNOs) are generally believed to take a most active part in many biological functions of nitric oxide especially in the processes of NO- storage, transport, and delivery. Numerous chemical and biological functions of RSNOs are being reported.[1,5]

Bartberger et al. showed that the conformational distribution of *S*-nitrosothiols dictate their spectroscopic behaviour.[6,7] Their observations found strong support from the experimental fact that *S*-nitrosothiols with primary alkyl groups are unstable and characterised only spectroscopically, whereas tertiary RSNOs have been isolated and are indefinitely stable. On the other hand Grossi et al.[8] reported that *S*-nitrosothiols undergo thermal decomposition at a rate independent of the bulkiness of the alkyl group. Lu et al. reported that the S–NO dissociation energies are ~20 kcal/mol when R is aryl but are ~28 kcal/mol when R is alkyl.[9] Recently we have reported the electronic structure of *S*-Nitrosothiols RS-NO in which relatively weaker σ bonds between S and N were observed.[10] These systems show very small S–N dissociation energies (20–28 kcal/mol) in spite of significant S–N partial double bond character (~11–13 kcal/mol for S–N rotational path). Natural Bond Orbital (NBO) analysis showed that $n_O \rightarrow \sigma^*_{S-N}$ interactions weaken the S–N σ bonds. Comparison of the S–N bond strength and second order electron delocalisations in MeS–NO with MeS–N=NH and MeS–$N=CH_2$ confirmed the importance of negative hyperconjugative interactions in these systems. It was argued that the weak sigma bonds are responsible for NO release from *S*-nitrosothiols.

Sulfoxidation is an important phenomenon under physiological conditions.[11] Drugs with thioether groups are known to undergo sulfoxidation during their metabolism. Single S-oxidation was shown to be reversible whereas double S-oxidation was shown to be irreversible under physiological conditions. Accordingly, *S*-nitrosothiols are probably also involved in S-oxidation under physiological conditions (eq. 1). If such a process is involved in the metabolism of *S*-nitrosothiols, the S–N bond strength in the oxidised form gets distorted and influences the NO releasing ability of *S*-nitrosothiols. In this paper we describe the

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Keywords: Ab initio; S-Nitrosothiols; Density functional; Negative hyper conjugative interaction; Nitric oxide.
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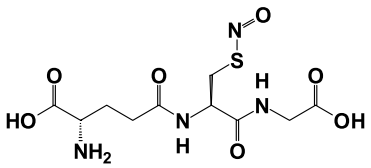

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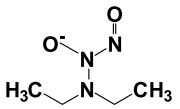

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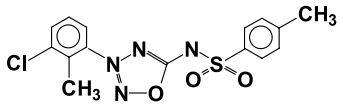
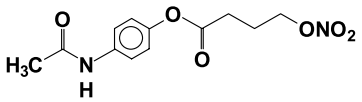
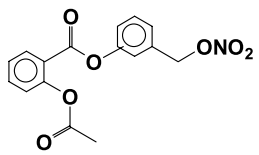


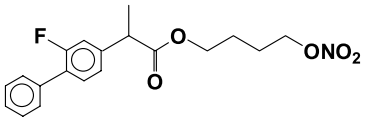
Mesoionic Oxatriazole



NO-Paracetamol

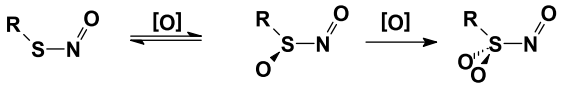


NO-Aspirin



NO-Fluribiprofen

electronic structure of **1**–**3** using ab initio MO and density functional methods, with the aim of estimating the variation in the S–N bond strength upon S-oxidation. A comparative study has been carried out between oxidised nitrosothiols vs oxidised sulfenamides[12] on the basis of bond length, bond order, bond dissociation energy and rotational barrier.



(1)

2. Methods of calculation

Ab initio molecular orbital (MO)[13] and Density functional calculations (DFT)[14] have been carried out using the GAUSSIAN98[15] package. Complete optimisations were performed on **1**, **2** and **3** their rotational barrier, bond dissociation energy (BDE) and corresponding transition states using the B3LYP/6-31+G*[16] and MP2(full)/6-31+G*[17] levels. All the minima are characterised by zero negative frequencies and the S–N rotational transition states are characterised by one negative frequency. Atomic charges in all the structures were obtained using the Natural Population Analysis (NPA) method within the Natural Bond Orbital (NBO) approach[18] using MP2(full)/6-31+G* geometries to understand the electron distribution in these molecules. Second order energy analysis has been carried out using the NBO method to understand the delocalisation present in oxidised nitrosothiols at MP2(full)/6-31+G* level. The bond orders have been calculated using Atoms In Molecules (AIM) method.[19] The MP2(full)/6-31+G* geometries and energies are employed in the discussion unless otherwise specifically mentioned.

3. Results and discussion

3.1. MeS-NO, 1

The absolute energies of methylnitrosothiol (**1**), its single and double oxidised derivatives (**2** and **3**) and their conformations isomers, including transition states, along the rotational path are given in Table 1. Figure 1 shows the important geometric parameters obtained at B3LYP/6-31+G* and MP2(full)/6-31+G* levels. On the potential energy (PE) surface of **1**, two minima and one transition state could be located. As described earlier,[6,7,10] the two isomers can be called *s-cis* and *s- trans* with respect to the S–N bond. This *cis–trans* isomerisation in **1** is due to the partial double bond between sulfur and nitrogen. The S–N bond length in the *cis* isomer **1c** is 1.761 Å at MP2(full)/6-31+G* level. The bond length estimated using B3LYP method is much longer at 1.827 Å. In the *trans* isomer **1t**, the S–N bond length gets slightly elongated to 1.775 Å at MP2 level. In the transition state **1-ts**, the S–N bond length gets much longer indicating breaking of the S–N π bond. The difference in the bond lengths in **1c** and **1ts** (i.e. 0.206 Å) can be considered as the contribution of the π bond towards S–N bond shortening in **1c**. The S–N bond length in **1c** (1.761 Å) is longer than the S–N bond length in sulfenamide, MeS–NH_2, **4** (1.730 Å). This is quite surprising because a system with a partial π bond (i.e. **1c**) has longer bond than a system (**4**) without such π bond, suggests that the S–N σ bond in **1c** must be much weaker than expected.

Table 1. Absolute energies (a.u.) of derivative of **1**, **2** and **3** obtained at B3LYP/6-31+G* and MP2(full)/6-31+G* levels

	B3LYP	MP2(FULL)
1c	−568.006896	−566.974188
1t	−568.006646	−566.973005
1ts	−567.985264	−566.954487
RS˙	−438.062562	−437.351002
NO	−129.895477	−129.577402
2a	−643.184221	−641.980819
2b	−643.178533	−641.974265
2c	−643.176735	−641.972183
2d	−643.175908	−641.971750
R(O)S˙	−513.283629	−512.390788
3a	−718.383247	−717.012439
3b	−718.382671	−717.010992
3c	−718.382498	−717.011282
3d	−718.380594	−717.009948
$R(O)_2S^{\cdot}$	−588.473619	−587.416757

The *trans* isomer **1t** is less stable than **1c** by about 1.56 kcal/mol (Table 2), this is in accordance with the earlier reports that the *trans* isomer should be less stable than the *cis* isomer.[10] Using NBO analysis, it was shown that the reason for the greater stability of **1c** may be attributed to $n_N \rightarrow \sigma^*_{S-C}$ negative hyperconjugative interaction (anomeric π interaction) in **1c** which is less pronounced in **1t**.[10] The S–N rotational barrier in **1c** is 12.4 kcal/mol, (Fig. 2(A)) indicating that the partial π bond in **1c** is fairly strong.

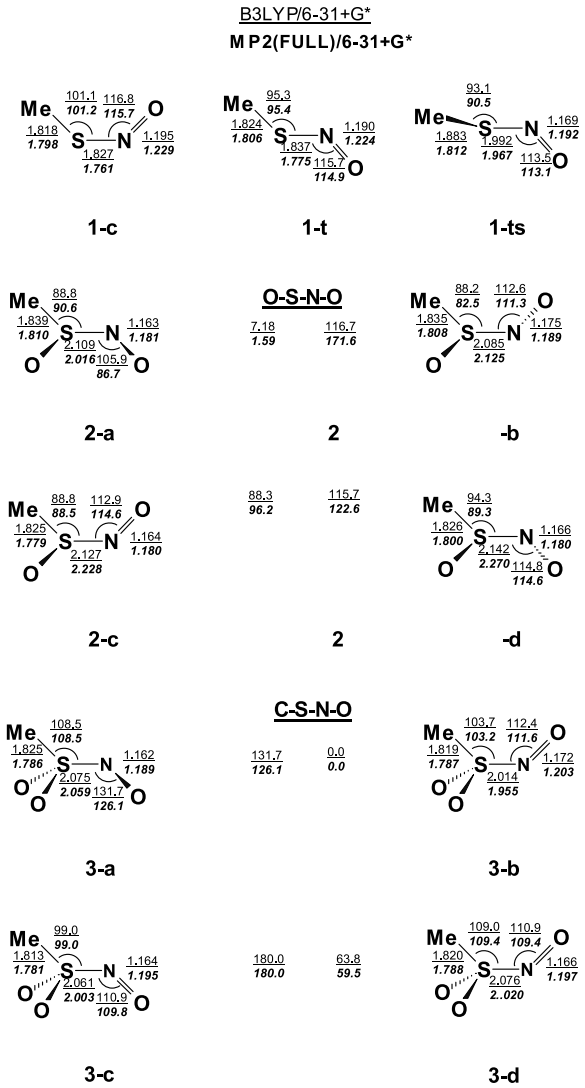


Figure 1. The important geometrical parameters and structures of different nitrosothiols derivatives. Distances in Å units and angles in degrees.

The S–N dissociation energy in **1c** is about 28.0 kcal/mol. This dissociation energy is much smaller than the S–N bond dissociation energy in $MeS–NH_2$ (68.7 kcal/mol), indicating that the S–N bond strength in *S*-nitrosothiol **1c** is very weak. This can be rationalised only when the basic sigma bond itself is very weak. NBO analysis suggests that there is a strong electron delocalisation from the $n_O \rightarrow \sigma^*_{S-N}$ bond in **1c**, which may be quantified in terms of the energy due to this second order interaction ($E^{(2)}$: 28.77 kcal/mol). The weaker σ bond in *S*-nitrosothiols may be attributed to this delocalisation of electron density, which is responsible for smaller dissociation energy and hence contributing to the nitric oxide releasing ability of these systems.

3.2. Me(O)S–NO, 2

On the S–N rotational surface of Me(O)S–NO, two minima (**2a** and **2b**) and two transition states (**2c** and **2d**) have been located. The two minima are defined by O–S–N–O torsional angles of ~0° and ~180° degrees. A structure with an O–S–N–O torsional angle of 0° has been found to be a global minimum at all levels, though this amounts to the presence of an eclipsed arrangement. The S–N single bond length in **2a** is 2.109 Å and 2.016 Å at B3LYP/6-31+G* and MP2(full)/6-31+G* levels respectively. On the other hand the S–N bond length at these two levels in **2b** is 2.085 and 2.125 Å respectively. The S–N bond length in **2** is much longer than that in **1**, this is presumably due to the absence of S–N π bond in **2**. The long S–N bond length in **2** indicates the very weak S–N interaction also. **2b** is less stable than **2a** by 3.5 kcal/mol at B3LYP level and 4.1 kcal/mol at MP2 level. The greater stability of **2a** with eclipsed arrangement can be attributed to $n_N \rightarrow \sigma^*_{S-O}$ negative hyperconjugative interaction, which is stronger than the $n_N \rightarrow \sigma^*_{S-C}$ negative hyperconjugative interaction in **2b**.

The two transition states (**2c** and **2d**) are characterised by O–S–N–O torsional angles of 96.2° and 122.6° at MP2 level. Figure 2(B) shows the PE surface of **2**. The overall energy barrier for S–N bond rotation is 5.6 kcal/mol at MP2 level. This value is much less than that in **1**. This reduction in the S–N rotational barrier upon oxidation can be attributed to the loss of S–N partial π bond between sulfur and nitrogen, as indicated by the bond length analysis also. The S–N dissociation energy in **2** is 7.9 kcal/mol at MP2 level, which is much smaller than that in **1** (28.0 kcal/mol). This supports the expectation that the S–N interaction is very weak in **2**. Such a weak S–N bond may be due to the weak sigma bond as in *S*-nitrosothiols. The energy due to the second order $n_{O(N)} \rightarrow \sigma^*_{S-N}$ negative hyperconjugative interaction in **2** is very large at 49.8 kcal/mol, weakening the S–N sigma bond. Compound **2** is also characterised by a $n_{O(S)} \rightarrow \sigma^*_{S-N}$ negative hyperconjgative interaction, thus explaining the smaller dissociation energy of **2** in relation to **1**.

3.3. $Me(O)_2S$–NO, 3

On the S–N rotational PE surface of **3**, (Fig. 2(C)) three minima and three transition states have been found. Out of the two minima, two are symmetric (both represented by **3a**)

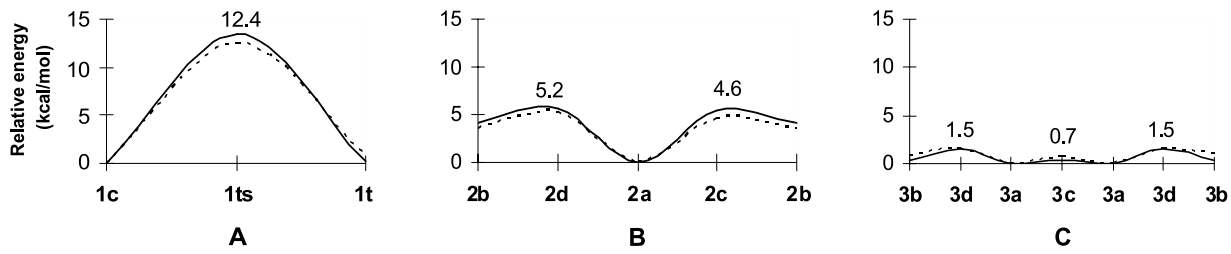


Figure 2. Graph showing the S–N rotational PE surfaces of **1**, **2** and **3** at B3LYP/6-31+G* (—) and MP2(full)/6-31+G* (- - -) levels. (MP2 values in kcal/mol reported).

Table 2. Relative energy (kcal/mol) of derivative of **1**, **2** and **3** obtained at B3LYP/6-31+G* and MP2(full)/6-31+G* levels

	B3LYP	MP2(FULL)
1c	0.0	0.0
1t	0.15	0.74
1ts	13.5	12.4
S–N BDE	30.6	28.7
2a	0.0	0.0
2b	3.5	4.1
2c	4.6	5.4
2d	5.2	5.6
S–N BDE	3.2	7.9
3a	0	0
3b	0.3	0.9
3c	0.4	0.7
3d	1.6	1.5
S–N BDE	8.8	11.4

Table 3. Second order delocalisation energies ($E^{(2)}$) in **1c**, **2a** and **3a** at MP2(full)/6-31+G* level

Structure	$E^{(2)a}$	$E_j-E_I^b$	F_{ij}^b
1c			
$n_S\rightarrow\pi^*_{N\text{-}O}$	43.79	0.46	0.127
$n_O\rightarrow\sigma^*_{S-N}$	28.77	0.85	0.140
2a			
$n_{O(S)}\rightarrow\sigma^*_{S-N}$	59.07	0.48	0.154
$n_{O(N)}\rightarrow\sigma^*_{S-N}$	49.79	0.62	0.163
3a			
$n_{O(N)}\rightarrow\sigma^*_{S-N}$	57.05	0.58	0.174
$n_{O(S)}\rightarrow\sigma^*_{S-N}$	47.24	0.46	0.139
$n_{O(S)}\rightarrow\sigma^*_{S-N}$	52.92	0.46	0.147

[a] kcal/mol.
[b] Atomic units.

with Me-S–N–O torsional angles of 126.1° and **3b** with an Me-S–N–O torsional angle of 0.0°. **3a** is more stable than **3b** by 0.3 kcal/mol at B3LYP/6-31+G* level and 0.9 kcal/mol at MP2(full)/6-31+G* level. All the minima on the PE surface show an eclipsed arrangement across the S–N bond. Even in this case, systems with O–S–N–O torsional angle of ~0° (ex. **3a**) have been found to be the most stable. The geometrical details of the minima on this PE surface show that all the minima contain an anti-periplanar arrangement between the lone pair on nitrogen and any of the S-X bonds. This suggests that the minima on this PE surface are stabilised by negative hyperconjugate interactions. The S–N bond length is 2.059 Å in **3a** and 1.955 Å in **3b**. These bond lengths are also much longer than the expected S–N single bond length. This clearly indicates the weakness of the S–N interaction. The S–N rotational barrier through the transition state **3d** is about 1.66 kcal/mol at B3LYP level and 1.56 kcal/mol at MP2 level, suggesting the absence of any π stabilisation. The S–N bond dissociation energy is about 8.8 kcal/mol at B3LYP level and 11.4 kcal/mol at MP2 level, suggesting a very weak S–N interaction. The decrease in the S–N rotational barrier and S–N dissociation energy in $R(O)_2S$–NO with respect to *S*-nitrosothiols can be expected because of the absence of partial double bond between S and N. NBO analysis suggests the presence of relatively strong $n_{O(N)}\rightarrow\sigma^*_{S-N}$ negative hyperconjugative interaction. ($E^{(2)}$: 57.05 kcal/mol in **3a** and 41.73 kcal/mol in **3b**). **3a** and **3b** also suffer from strong $n_{O(S)}\rightarrow\sigma^*_{S-N}$ delocalisations (Table 3). These interactions increase the electron density in the σ^* orbital across S–N bond and hence weaken the S–N σ bond. The above analysis indicates that the double oxidation at sulfur decreases the S–N strength and hence facilitates the release of nitric oxide.

Comparative data related to the S–N bond lengths, bond orders, bond dissociation energies and rotational barrier values for **1**–**6** are given in Table 4. The AIM estimated bond orders for S–N bond in **1**–**3** respectively are 0.949, 0.642 and 0.784. The S–N bond dissociation energies follow the same order: 18.0, 7.9 and 11.4 kcal/mol. This clearly suggests that single oxidation greatly decreases the S–N strength. Though double oxidation recovers the S–N strength partially, it is not sufficient to bring it back to the level of *S*-nitrosothiols. The S–N bond lengths, bond orders, rotational barriers and bond dissociation energies of methylsulfenamide (Me-S–NH_2), **4** methylsulfinamide (Me-S(O)–NH_2), **5** and methylsulfonamide (Me-$S(O)_2$–NH_2), **6** obtained at MP2(full)/6-31+G* level are also given in Table 4 for comparison purpose. These data indicate that the S–N bond strength in these systems (**4**–**6**) is very strong. In the case of methylsulfenamide also single oxidation decreases the S–N bond strength, though S–N bond length decreases. Comparison of data in an NO series (i.e. **1**–**3**) with the NH_2 series (i.e. **4**–**6**) suggests that the observed S–N bond weakening should be attributed to the oxygen atom of the nitroso group, which is weakening the S–N sigma bond because of strong $n_O\rightarrow\sigma^*_{S-N}$ delocalisation. The NO release from *S*-nitrosothiols under physiological conditions might be following the reversible S-oxidation pathway which strongly facilitates the NO release.

Table 4. Various calculated parameters associated with S–N bond in S-nitrosothiol **1** and Sulfonamide **4** and their oxidised derivative

Structure	Bond length[a]	Bond order	Rotational barrier[b]	Dissociation energy[b]
Me-S–NO(**1**)	1.761	0.949	12.4	28.0
Me-S(O)–NO(**2**)	2.016	0.642	5.6	7.9
Me-$S(O)_2$–NO(**3**)	2.059	0.784	1.5	11.4
Me-S–NH_2(**4**)	1.730	0.971	8.17	68.7
Me-S(O)–NH_2(**5**)	1.715	0.896	5.88	61.7
Me-$S(O)_2$–NH_2(**6**)	1.683	0.856	7.53	73.5

[a] Angstroms units.
[b] kcal/mol.

4. Conclusions

Ab initio MO and DFT calculations on **1**, **2** and **3** at different levels showed that the changes observed in S–N bond lengths, S–N bond order, S–N bond rotational barrier and S–N bond dissociation energies indicate that the S–N bond is very weak in these systems. The weakness in the S–N bond originates from the negative hyperconjugative interactions in these systems. The weakness increases upon single oxidation from **1** and **2**. Though some recovery of S–N strength was observed upon double oxidation, it is very small. Single oxidation in **1** decrease the S–N dissociation energy from 28.0 to 7.9 kcal/mol, suggesting that the NO release in *S*-nitrosothiols may be triggered by reversible S-oxidation in *S*-nitrosothiols under physiological conditions.

Acknowledgements

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Highly diastereoselective Henry reaction of nitro compounds with chiral derivatives of glyoxylic acid

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Abstract—*N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam and (1*R*)-8-phenylmenthyl glyoxylate react stereoselectively with simple nitro compounds giving diastereoisomeric nitroalcohols with high asymmetric induction. *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam **1a** is shown to be a highly efficient chiral inducer, superior to (1*R*)-8-phenylmenthyl glyoxylate **1b**. In all cases, the absolute (2*S*) configuration at the center bearing the hydroxy group and the relative *syn* configuration for the major diastereoisomers were determined.

1. Introduction

The nitroaldol addition is one of the basic methods for the construction of carbon–carbon bonds.[1] The nitroalcohols formed in this reaction offer an easy access to a variety of interesting intermediates such as 2-aminoalcohols, 2-nitroketones and nitroalkenes,[2] which are useful for the synthesis of biologically important compounds.[3] Currently, there is a substantial interest in the development of a stereocontrolled version of the Henry reaction. The chiral building block approach has been widely investigated,[4] however, particular attention was paid to application of chiral catalysts, providing nitroalcohols in good yield and with high enantioselectivity.[5] On the other hand, there are only two examples of the diastereoselective Henry reaction using substrates containing a chiral auxiliary, namely (1*R*)-8-phenylmenthol, in the literature.[6]

In the course of our search for synthetic applications of chiral derivatives of α-oxo acids, we have synthesised *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**1a**)[7] and examined its applicability in a number of diastereoselective reactions.[8] High asymmetric induction obtained during these studies prompted us to extend our investigations on addition of **1a** to nitromethane (**2**) and five other simple nitro compounds of type **3**, and to compare the efficiency of **1a** with that of the glyoxylic ester of (1*R*)-8-phenylmenthol (**1b**) (Scheme 1).

2. Results and discussion

Initial investigations on the reaction of **1a** with nitromethane (**2**), carried out under conditions described by Solladié-Cavallo et al.[6] for glyoxylate **1b** failed completely giving only products from fragmentation of bornane-10-2-sultam despite the temperature of the reaction. Due to these results, we excluded potassium fluoride, common mediator of the nitroaldol reaction. To overcome this problem, we resolved to check two other procedures using either neutral Al_2O_3 (Method A) or tetrabutylammonium fluoride trihydrate (TBAF·$3H_2O$, Method B).

As revealed in Table 1, only moderate yields were obtained for the reactions promoted by both Al_2O_3 and TBAF·$3H_2O$ (Table 1, entries 1 and 3), and substantial amounts of sultam auxiliary were found in reaction mixtures. However, these reactions proceeded with high diastereoselectivity. Encouraged by these results, we decided to improve the reaction yields by using Al_2O_3 activated by heating at 120 °C under reduced pressure (Method A′) or anhydrous TBAF dried at 80 °C in vacuum (Method B′).

Indeed, we obtained much better yields for the reactions under investigation. We also checked the influence of high pressure on the reaction course. Unfortunately, we did not observed an increase of the chemical yield as we expected (entry 5). At the next stage of our studies, we studied five other nitro compounds, namely 1-nitrohexane (**3a**), 2-nitroacetaldehyde diethyl acetal (**3b**), 1-nitro-1-phenylmethane (**3c**), 2-nitro-1-phenylethane (**3d**) and ethyl nitroacetate (**3e**). We have chosen them among others as a representative group made of simple aliphatic, benzylic or

Keywords: Nitroalcohols; Nitroaldol reaction; Asymmetric induction; Nitro compounds; Chiral auxiliary.
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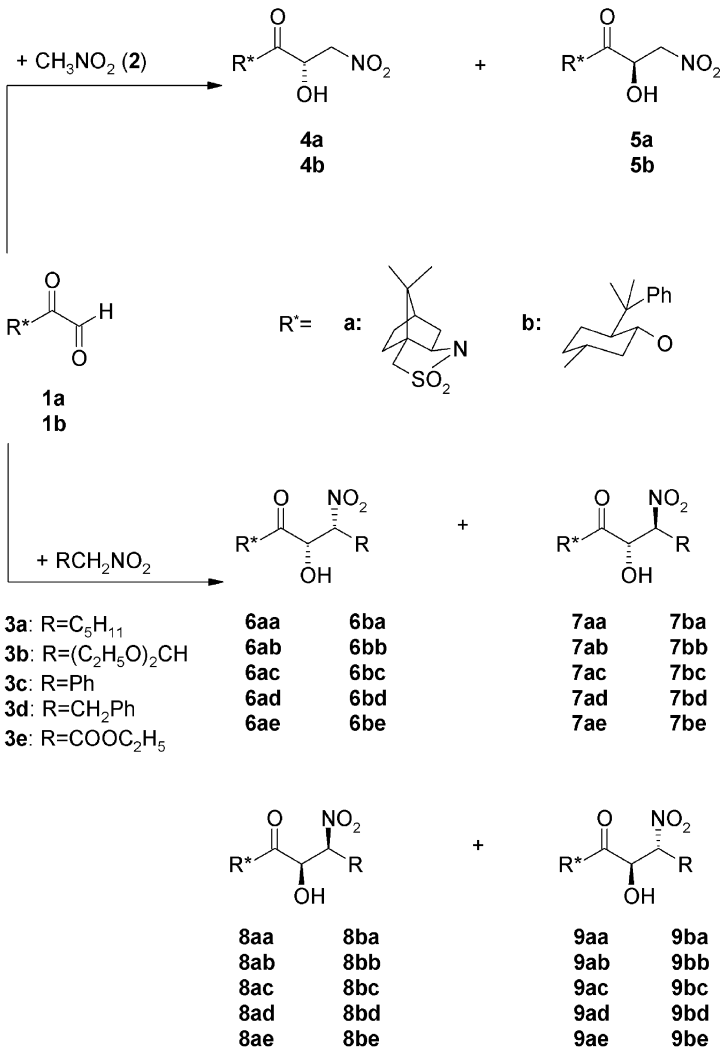


Scheme 1.

having functional groups, which open routes to further functionalisation of the obtained products. Four diastereoisomeric nitroalcohols were formed upon their reaction with **1a** (Scheme 1, Table 2).

Similarly to the reactions of **1a** with **2** (Table 1), application of the activated catalysts highly improved the yield of reactions of **3a-e** with **1a**, although unfortunately were accompanied by a slight decrease of diastereoselectivity (Table 2, Methods A′ and B′). The only exception is the product **6ab** which was detected to be a single diastereoisomer (entries 8–10). The reactions of **3b** and **3c** carried out under high pressure provided the nitroalcohols with much higher yields (entries 10 and 15). As regards diastereoselectivity, we observed formation of four possible diastereoisomers; in most cases we were able to isolate and characterise them in a chromatographically pure form. The best results were obtained for the reaction of **1a** with **3b**, when a single diastereoisomer was formed (entry 9).

Table 1. Reactions of chiral aldehyde **1a** with **2**

Entry	Method[a]	Time (h)	Yield[b] (%)	Diastereoisomeric ratio[c] **4a**:**5a**
1	A	48	30	83:17
2	A′	4	80	77:23
3	B	2	38	97:3
4	B′	8	50	98:2
5	C	2.5	28	90:10

[a] Method A: Al_2O_3, rt; A′: activated Al_2O_3, rt, B: TBAF·$3H_2O$, −78 °C; B′: anhydrous TBAF, −78 °C; C: TBAF·$3H_2O$, 10 kbar, 0 °C.
[b] Yield given for isolated products.
[c] Calculated by both HPLC and ^{1}H NMR analysis

The second chiral auxiliary applied by us was (1*R*)-8-phenylmenthol which earlier proved to be very effective in many other processes, especially in aldol condensations which is similar to the Henry reaction.[9] Its glyoxylate **1b**, being an ester, was supposed to be more stable than glyoximide **1a** under the reaction conditions. Presumably for the initial reactions of glyoxylate **1b** with nitromethane (**2**) we did not notice any influence of the way of preparing catalysts on the chemical yield; the ester moiety did not hydrolyse. Both TBAF and Al_2O_3 led to the desired nitroalcohols in high yields, however, the use of activated catalysts improved slightly their efficiency (Table 3).

Table 2. Reactions of chiral aldehyde **1a** with nitro compounds **3a-e**

Entry	Nitro compound	Method[a] used	Time (h)	Yield[b] (%)	Diastereoisomeric ratio[c] **6**:**7**:**8**:**9**
1	**3a**	A	26	5	74:26:0:0
2	**3a**	A′	8	93	68:14:12:6
3	**3a**	B	2	29	90:10:0:0
4	**3a**	B′	2,5	38	54:33:7:7
5	**3a**	C	2.5	28	88:12:0:0
6	**3b**	A	26	0	—
7	**3b**	A′	1	78	64:16:15:5
8	**3b**	B	5	45	>99:1:0:0
9	**3b**	B′	2.5	80	>99:1:0:0
10	**3b**	C	3	70	>99:1:0:0
11	**3c**	A	2.5	46	84:16:0:0
12	**3c**	A′	0.5	90	75:20:5:0
13	**3c**	B	2.5	42	93:7:0:0
14	**3c**	B′	1.5	82	88:7:5:0
15	**3c**	C	3	60	92:8:0:0
16	**3d**	A′	1	91	59:19:16:6
17	**3d**	B	1	6	—
18	**3d**	B′	8	50	57:20:13:10
19	**3e**	A	24	55	38:30:21:11
20	**3e**	A′	1.5	83	39:26:23:12
21	**3e**	B	2	43	34:26:25:15
22	**3e**	B′	2	70	35:30:21:14
23	**3e**	C	2	41	31:23:28:18

[a] Method A: Al_2O_3, RT; A′: activated Al_2O_3, rt, B: TBAF·$3H_2O$, −78 °C; B′: anhydrous TBAF, −78 °C; C: TBAF·$3H_2O$, 10 kbar, 0 °C.
[b] Calculated by both HPLC and ^1H NMR analysis.
[c] Yield given for isolated products.

The same relationships were observed for reactions of **1b** with other nitro compounds **3a-e** (Table 4). As far as diastereoselectivity is concerned, we found that (1*R*)-8-phenylmenthol is a less efficient chiral auxiliary compared to (2*R*)-bornane-10,2-sultam. In most cases, we observed formation of four possible diastereoisomers. Additionally, the reactions catalysed by TBAF provided the products in lower diastereoselectivity than the corresponding reactions catalysed by Al_2O_3. Similarly to the reactions of **1a**, application of activated Al_2O_3 resulted in a slight decrease of diastereoselectivity (Table 4, Method A′). Lowering the temperature of the above processes resulted in formation of nitroalcohols with better chiral induction as well as high chemical yields (entries 16–18). In general, the use of **1a**, as compared with **1b**, led to better stereochemical results.

The configuration of major diastereoisomer **4a** was established on the basis of correlation between optical rotations of nitrodiol **10**, the product of reductive removal of chiral auxiliary, and the analogous nitrodiol of known stereochemistry, which was obtained from reduction of adduct **4b** (Scheme 2). The configuration of compound **4b** was set up as (2*S*) via its chemical correlation to L-isoserine, as described later.

Table 3. Reactions of chiral aldehyde **1b** with **2**

Entry	Method[a]	Time (h)	Yield[b] (%)	Diastereoisomeric ratio[c] **4b**:**5b**
1	A	17	78	85:15
2	A′	24	90	73:27
3	B	5.5	43	53:47
4	B′	2.5	86	75:25
5	C	3	75	73:27

[a] Method A: Al_2O_3, rt; A′: activated Al_2O_3, rt, B: TBAF·$3H_2O$, −78 °C; B′: anhydrous TBAF, −78 °C; C: TBAF·$3H_2O$, 10 kbar, 0 °C.
[b] Yield given for the isolated products.
[c] Calculated by both HPLC and ^1H NMR analysis.

An X-ray analysis was made for the major adduct **6aa**, showing the absolute (2*S*) configuration at the center bearing the hydroxy group, and the relative *syn* configuration of hydroxy and nitro groups (Fig. 1).

The configuration of the minor diastereoisomer **7aa** was estimated by comparison of optical rotations and NMR spectra of two nitrodiols **11a** and **11b** obtained by reductive hydrolysis of sultam from diastereoisomerical diols (2*S*)-**6aa** and **7aa** (Scheme 3). Nitrodiols **11a** and **11b** were in diastereoisomeric relationship, that is, the relative configuration of compound **7aa** is *anti*.

The configuration of major adduct **6ab**, was determined by the X-ray crystal structure. As revealed in Figure 2, it has the absolute (2*S*)-hydroxy-(3*R*)-nitro configuration, which constitutes a relative *syn* relation (Fig. 2).

In the case of the adduct obtained in the reaction of **1a** with 1-nitro-1-phenylmethane (**3c**), the major diastereoisomer **6ac** shows the (2*S*)-hydroxy-(3*R*)-nitro absolute configuration and the relative *syn* configuration as established earlier by X-ray analysis.[10] Configurations of minor products were assigned on analogous way as in the case of nitroalcohols **6aa** and **7aa** (Scheme 3).

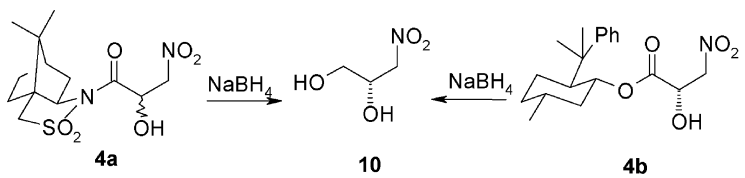
The configuration of compound **4b** was established as (2*S*) from its chemical correlation to (−)-isoserine (**14**) (Scheme 4).[6] Nitroalcohol **4b**, after protecting its hydroxy group with *t*-butyldimethylsilyl chloride, was catalytically reduced to give amine **13**, which was converted to (−)-**14** by simultaneous hydrolysis of chiral auxiliary and protecting group.

The configuration of two major products formed in the reaction of **1b** with 1-nitrohexane (**3a**) were estimated by measurements of NOE for H-2 and H-3 hydrogens of

Table 4. Reactions of chiral aldehyde **1b** with nitro compounds **3a-e**

Entry	Nitro compound	Method[a] used	Time (h)	Yield[b] (%)	Diasteroisomeric ratio[c] **6**:**7**:**8**:**9**
1	**3a**	A	17	60	62:22:10:6
2	**3a**	A′	24	85	58:24:12:6
3	**3a**	B	22	43	34:30:24:12
4	**3a**	B′	1	90	33:28:23:16
5	**3a**	C	2	73	42:24:20:14
6	**3b**	A	17	39	88:7:5:0
7	**3b**	A′	6	96	68:21:8:3
8	**3b**	B	2	47	62:17:15:6
9	**3b**	B′	1	64	66:24:10:0
10	**3b**	C	2	62	61:17:15:7
11	**3c**	A	3	90	89:8:3:0
12	**3c**	A′	1	97	83:13:0:0
13	**3c**	B″	1.5	90	63:23:14
14	**3c**	B	20	86	51:35:14
15	**3c**	C	2	77	66:23:11
16	**3d**	A	48	60	47:32:14:7
17	**3d**	A′	7	98	62:19:13:6
18	**3d**	A″	24	89	71:19:6:5
19	**3d**	B	2.5	97	28:27:26:18
20	**3e**	A	20	95	54:46:0:0
21	**3e**	B	5	96	50:50:0:0
22	**3e**	C	2	98	50:50:0:0

[a] Method A: Al_2O_3, RT; A′: activated Al_2O_3, RT, A″: activated Al_2O_3, −20 °C, B: TBAF·3H_2O, −78 °C; B′: 0.5 anhydrous TBAF, −78 °C; B″: TBAF·3H_2O, −20 °C; C: TBAF·3H_2O, 10 kbar, 0 °C.
[b] Calculated by HPLC analysis and ^{1}H NMR.
[c] Yield given for isolated products.



Scheme 2.

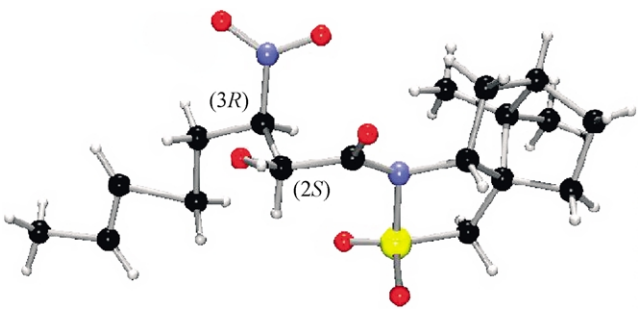
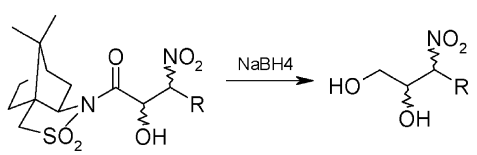


Figure 1. X-ray structure of (2′R)-*N*-[(2*S*)-hydroxy-(3*R*)-nitrooctanoyl]-bornane-10′,2′-sultam (**6aa**).



6aa	R=C_5H_{11}	**11a**
7aa	R=C_5H_{11}	**11b**
6ac	R=Ph	**12a**
7ac	R=Ph	**12b**
8ac	R=Ph	**12c**

Scheme 3.

isopropylidene derivatives **18a** and **18b**, produced from adducts **6ba** and **7ba**, respectively (Scheme 5). Positive NOE was observed for the oxazolidine **18b** (10.0% for H-2, 7.6% for H-3) indicating the relative *syn* configuration of H-2 and H-3 hydrogens, which determine relative configuration *anti* for compound **7ba**. The positive NOE was not seen for the oxazolidine **18a**, pointing out the relative *anti* configuration of H-2 and H-3, which states the relative *syn* configuration for compound **6ba**.

The same procedure was applied for assignment of the relative configuration of nitroalcohols **6bb**, **7bb** and **7bc** (Scheme 5).

In the case of the adduct obtained in the reaction of **1b** with 1-nitro-1-phenylmethane (**3c**), the major diastereoisomer **6bc** shows the (2*S*)-hydroxy-(3*R*)-nitro configuration and the relative *syn* configuration for these groups established earlier by X-ray analysis.[10] That compound was used in the total synthesis of Taxotere® side chain.[11]

In the case of the adduct obtained in the reaction of **1b** with 2-nitro-1-phenylethane (**3d**), the configuration of the major diastereoisomer **6bd** was established as (2*S*,3*R*) by total synthesis of (−)-bestatin.[11] The configuration of the minor diastereoisomer **7bd**, assigned earlier by X-ray analysis, is

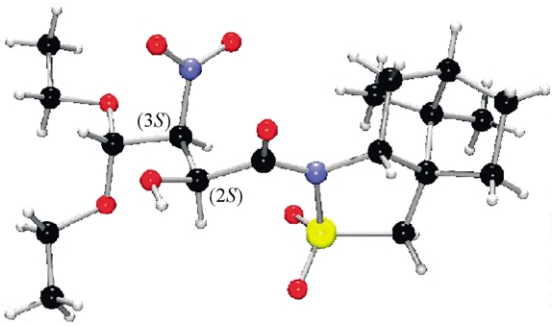


Figure 2. X-ray structure of (2′*R*)-N-[4,4-Diethoxy-(2*S*)-hydroxy-(3*R*)-nitrobutanoyl]-bornane-10′,′2-sultam (**6ab**).

(2*S*)-hydroxy-(3*S*)-nitro and the relative configuration of these groups is *anti*.[10]

On the basis of structural analysis referring to relationship of configurations of new stereogenic centres, we have noticed the occurrence of some distinct regularities. The most important one is that the major diastereoisomer obtained in the above-discussed reactions has the relative *syn* configuration of nitro and hydroxy groups, and the absolute (2*S*)-hydroxy-(3*R*)-nitro configuration. The second diastereoisomer formed also possess the absolute configuration (2*S*), however the relative relation of C-2 and C-3 substituents was in all cases *anti*.

3. Conclusions

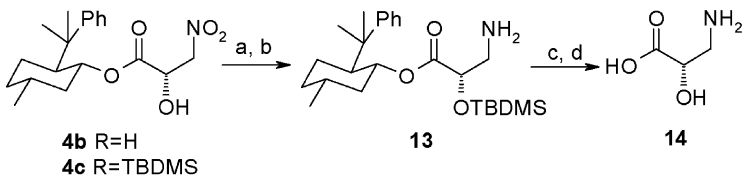
On the basis of the above-mentioned analyses, we conclude that the major diastereoisomers **4** and **6** possess the absolute (2*S*) configuration of the hydroxy-bearing stereogenic centre in all cases. The relative configuration of nitro and hydroxy groups is *syn* for all major diastereoisomers **6**, contrary to the *anti* configuration found in products obtained via the chiral-pool approach. Thus, our methodology seems to be complementary to the chiral pool as concerns the relative configuration of newly created stereogenic centres.

In summary, we have shown that the derivatives of glyoxylic acid, bearing (2*R*)-bornane-10,2-sultam and (1*R*)-8-phenylmenthol as chiral auxiliaries, are very convenient substrates for preparation of optically pure nitro-alcohols that could be used as starting materials in the synthesis of various natural products.

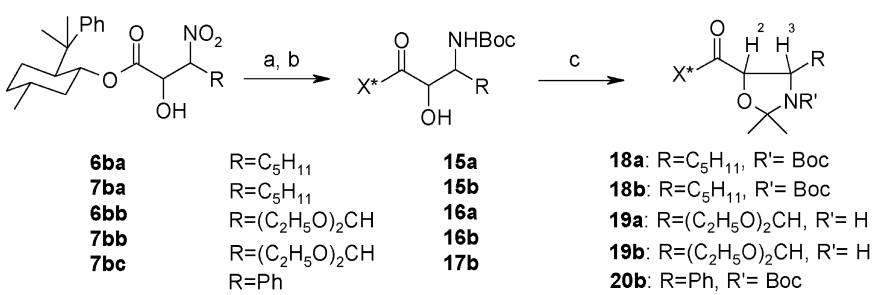
4. Experimental

4.1. General methods

All reactions were carried out under argon atmosphere with anhydrous solvents dried according to standard laboratory methods. ^{1}H and ^{13}C NMR spectra were measured on Bruker AM-500 (500 and 125 MHz, respectively) and Varian Gemini (200 and 50 MHz, respectively) spectrometers using residual $CHCl_3$ as internal reference. Mass spectra were carried out with AMD-604 Intectra instrument. Optical rotations were measured on a JASCO DIP-360 polarimeter with a thermally jacketed 10 cm cell. Infrared spectra were recorded on a Perkin–Elmer 1640 FT-IR. Melting points were determined with Kofler hot stage apparatus and are uncorrected. Flash-column chromatography was performed on silica gel (Kieselgel-60, Merck, 200–400 mesh). TLC was performed on Merck aluminum plates (Kieselgel 60 F_{254}) and compounds were visualized with a solution of MoO_3 and $Ce_2(SO_4)_3$ in 15% H_2SO_4. All high-pressure reactions were carried out in a piston-cylinder type apparatus with an initial working volume of about 5 mL. The X-ray measurements were run on a Nonius MACH3 diffractometer using Express software, without absorption corrections. The structures were solved by the SHELXS86[12] and refined with the SHELXL93[13] programs. The known configuration of the asymmetric centres has been confirmed by the Flack parameter refinement. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers **6aa**: CCDC 228305 and **6ab**: CCDC 228306. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2



Scheme 4. Reagents: (a) TBDMSCl, (b) H_2, Raney Ni, (c) HCl, (d) epoxypropane



Scheme 5. Reagents: (a) H_2, Raney Ni, (b) Boc_2O, (c) DMP, H^+.

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4.2. General procedures for the reactions of 1 with 2 or 3

4.2.1. General procedure for the neutral Al_2O_3 (Method A) or activated Al_2O_3 (Method A′) catalysed reaction. A carbonyl compound (1 mmol) and a nitro compound (2 mmol) were added to a solution of a catalyst (2 mmol) in THF (5 mL) at rt under argon atmosphere. Activated Al_2O_3 was prepared before the reaction by heating at 120 °C under reduced pressure (0.2 mm Hg) for 2 h. The reaction was monitored by TLC, and when finished, it was filtered and evaporated. All products were purified by column chromatography (hexane/AcOEt 9:1–6:4).

4.2.2. General procedure for the TBAF·3H$_2$O (Method B) and TBAF (Methods B′ and B″) catalysed reaction. A catalyst (0.5 mmol) was added to a solution of a carbonyl compound (1 mmol) in dry THF (5 mL) under argon atmosphere. The reaction mixture was cooled to −78 °C and a nitro compound (2 mmol) was added. Anhydrous TBAF was prepared just before the reaction by heating at 80 °C at reduced pressure (0.2 mm Hg) for 2 h. The reaction was monitored by TLC, and when finished, it was quenched by addition of saturated aqueous NaCl and extracted with AcOEt. The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated. All products were purified by column chromatography (hexane–AcOEt 9:1–6:4).

4.2.3. General procedure for the TBAF·3H$_2$O catalysed reaction under high pressure (10 kbar) (Method C). A catalyst (0.5 mmol) was added to a precooled (0 °C) solution of a carbonyl compound (1 mmol) in dry THF (5 mL), followed by addition of a nitro compound (2 mmol). The reaction was carried out in high pressure apparatus at the indicated temperature and time. When finished, it was quenched by addition of saturated aqueous NaCl and extracted with AcOEt. The combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated. All products were purified by column chromatography (hexane/AcOEt 9:1–6:4).

4.2.4. (2′*R*)-*N*-[(2*S*)-Hydroxy-3-nitropropanoyl]-bornane-10′,2′-sultam (4a). Colourless crystals, mp=160–161 °C (MeOH); HRMS-EI: Calcd for $C_{13}H_{20}O_6N_2SNa$ $(M+Na)^+$: 355.0939, found 355.0942. Anal Calcd C. 46.97, H. 6.08, N. 8.42, S. 9.64, found C. 47.18, H. 6.14, N. 8.33, S. 9.71; IR (KBr): 3492, 2964, 2884, 1694, 1549, 1329, 1296, 1222, 1138, 1101, 1064, 769, 611, 533 cm^{-1}; $[\alpha]_D^{20}=-103.6$ (c=0.90; $CHCl_3$); R_f=0.5 (hexane/AcOEt 6:4); ^{1}H NMR (400 MHz; $CDCl_3$): δ 5.11 (ddd, $J_{2,3A}$=3.9 Hz, $J_{2,3B}$=4.0 Hz, $J_{2,OH}$=5.9 Hz, 1H, H-2), 5.01 (dd_{AB}, $J_{3A,3B}$=13.3 Hz, $J_{2,3A}$=3.9 Hz, 1H, H_A-3), 4.88 (dd_{AB}, $J_{3A,3B}$=13.3 Hz, $J_{2,3B}$=4.0 Hz, 1H, H_B-3), 4.00 (dd, $J_{2',3'A}$=4.7 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′), 3.77 (d, $J_{2,OH}$=5.9 Hz, 1H, OH), 3.56 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 3.52 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 2.21 (ddd, $J_{2',3'A}$=4.7 Hz, $J_{3'A,3'B}$=13.8 Hz, $J_{3'A,4}$=7.3 Hz, 1H, H_A-3′), 2.09 (dd, $J_{2',3'B}$=7.8 Hz, $J_{3'A,3'B}$=$J_{3'A,4}$=13.8 Hz, 1H, H_B-3′), 2.00–1.84 (m, 3H, H-4′, H-6′), 1.51–1.25 (m, 2H, H-5′), 1.13 (s, 3H, H-8′), 0.99 (s, 3H, H-9′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 169.9 (C-1), 78.3 (C-3), 68.4 (C-2), 65.4 (C-2′), 52.8 (C-10′), 49.3 (C-1′), 48.0 (C-7′), 44.4 (C-4′), 37.3 (C-3′), 32.6 (C-6′), 26.3 (C-5′), 20.3 (C-8′), 19.8 (C-9′).

4.2.5. (2′*R*)-*N*-[(2′*R*)-Hydroxy-3-nitropropanoyl]-bornane-10′,2′-sultam (5a). Selected signals from differential NMR spectra: ^{1}H (400 MHz; $CDCl_3$): δ 5.33 (ddd, $J_{2,3A}$=4.0 Hz, $J_{2,3B}$=8.0 Hz, $J_{2,OH}$=6.4 Hz, 1H, H-2), 4.90 (dd_{AB}, $J_{3A,3B}$=14.0 Hz, $J_{2,3A}$=4.0 Hz, 1H, H_A-3), 4.69 (dd_{AB}, $J_{3A,3B}$=14.0 Hz, $J_{2,3B}$=8.0 Hz, 1H, H_B-3), 3.93 (dd, $J_{2',3'A}$=4.8 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′), 3.84 (d, $J_{2,OH}$=6.4 Hz, 1H, OH), 3.59 (d_{AB}, $J_{10'A,10'B}$=13.9 Hz, 1H, H_A-10′), 3.55 (d_{AB}, $J_{10'A,10'B}$=13.9 Hz, 1H, H_A-10′), 1.14 (s, 3H, H-8′), 0.93 (s, 3H, H-9′); ^{13}C (50 MHz; $CDCl_3$): δ 168.8 (C-1), 75.6 (C-3), 68.1 (C-2), 65.2 (C-2′), 52.6 (C-10′), 49.5 (C-1′), 47.9 (C-7′), 44.6 (C-4′), 37.4 (C-3′), 32.7 (C-6′), 26.4 (C-5′), 20.4 (C-8′), 19.9 (C-9′).

4.2.6. (2′*R*)-*N*-[(2*S*)-Hydroxy-(3*R*)-nitrooctanoyl]-bornane-10′,2′-sultam (6aa). Colourless crystals, mp=79–80 °C (hexane/AcOEt); HRMS-EI: Calcd $C_{18}H_{31}N_2O_6S$ $(M+H)^+$: 403.1902, found 403.1923. Anal Calcd C. 53.71, H. 7.51, N. 6.96, S. 7.97, found C. 53.71, H. 7.54, N. 7.00, S. 7.89; IR (KBr): 3493, 3291, 2959, 2932, 2877, 1696, 1555, 1334, 1292, 1216, 1136, 1051, 765, 627, 536 cm^{-1}; $[\alpha]_D^{20}=-66.7$ (c=1.05; $CHCl_3$); R_f=0.6 (hexane/AcOEt 7:3); ^{1}H NMR δ (500 MHz; $CDCl_3$): δ 5.02 (ddd, $J_{2,3}$=2.4 Hz, $J_{3,4A}$=5.9 Hz, $J_{3,4B}$=8.4 Hz, 1H, H-3), 4.91 (dd, $J_{2,3}$=2.4 Hz, $J_{2,OH}$=7.8 Hz, 1H, H-2), 3.97 (dd, $J_{2',3'A}$=4.7 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′), 3.55 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 3.50 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_B-10′), 3.44 (d, $J_{2,OH}$=7.8 Hz, 1H, OH), 2.31–2.23 (m, 2H, H-4), 2.20 (ddd, $J_{2',3'A}$=4.7 Hz, $J_{3'A,4}$=7.8 Hz, $J_{3'A,3'B}$=14.0 Hz, 1H, H_A-3′), 2.20 (dd, $J_{2',3'B}$=$J_{3'A,4}$=7.8 Hz, $J_{3'A,3'B}$=14.0 Hz, 1H, H_B-3′), 2.00–1.85 (m, 3H, H-4′, H-6′), 1.51–1.28 (m, 8H, H-5, H-6, H-7, H-5′), 1.22 (s, 3H, H-8′), 1.00 (s, 3H, H-9′), 0.89 (t, 3H, $J_{7,8}$=7.0 Hz, H-8); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3(C-1), 89.4 (C-3), 71.4 (C-2), 65.2 (C-2′), 52.8 (C-10′), 49.1 (C-1′), 47.9 (C-7′), 44.3 (C-4′), 37.3 (C-3′), 35.9 (C-6′), 31.2 (C-4), 29.2 (C-5), 26.7 (C-5′), 24.9 (C-6), 22.1 (C-7), 20.3 (C-8′), 19.8 (C-9′), 13.8 (C-8).

4.2.7. (2′*R*)-*N*-[*anti*-(2ξ)-Hydroxy-(3ξ)-nitrooctanoyl]-bornane-10′,2′-sultam (7aa). Colourless oil, $[\alpha]_D^{20}=-63.6$ (c=0.845; $CHCl_3$); R_f=0.5 (hexane/AcOEt 7:3); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.26 (dd, $J_{2,3}$=5.4 Hz, $J_{2,OH}$=6.3 Hz, 1H, H-2), 4.92 (ddd, $J_{2,3}$=5.4 Hz, $J_{3,4A}$=3.3 Hz, $J_{3,4B}$=9.1 Hz, 1H, H-3), 3.96 (dd, $J_{2',3'A}$=4.9 Hz, $J_{2',3'B}$=7.7 Hz, 1H, H-2′), 3.58 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 3.51 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_B-10′), 3.50 (d, $J_{2,OH}$=6.3 Hz, 1H, OH), 2.18–1.70 (m, 7H, H-4, H-3′, H-4′, H-6′), 1.49–1.23 (m, 8H, H-5, H-6, H-7, H-5′), 1.15 (s, 3H, H-8′), 1.01 (s, 3H, H-9′), 0.87 (t, 3H, $J_{7,8}$=6.8 Hz, H-8); ^{13}C NMR (125 MHz; $CDCl_3$): δ 169.5 (C-1), 87.3 (C-3), 70.8 (C-2), 65.3 (C-2′), 52.9 (C-10′), 49.2 (C-1′), 47.9 (C-7′), 44.5 (C-4′), 37.9 (C-3′), 32.8 (C-6′), 31.2 (C-4), 27.8 (C-5), 26.3 (C-5′), 25.1 (C-6), 22.2 (C-7), 20.6 (C-8′), 19.8 (C-9′), 13.8 (C-8).

4.2.8. (2′*R*)-*N*-[4,4-Diethoxy-(2*S*)-hydroxy-(3*S*)-nitrobutanoyl]-bornane-10′,′2-sultam (6ab). Colourless crystals, mp=98–100 °C (hexane/Et_2O); HRMS-EI: Calcd

for $C_{18}H_{30}N_2O_8SNa$ $(M+Na)^+$ 457.1620, found 457.1608. Anal Calcd C. 49.76, H. 6.96, N. 6.45, S. 7.38, found C. 49.95, H. 7.25, N. 6.53, S. 7.54; IR (KBr): 3527, 3291, 2966, 1686, 1553, 1333, 1142, 1064 cm^{-1}; $[\alpha]_D{}^{20}=-75.6$ (c=1.03; $CHCl_3$); R_f=0.6 (hexane/AcOEt 7:3); ^1H NMR (200 MHz; $CDCl_3$): δ 5.24 (d, $J_{3,4}$=8.2 Hz, 1H, H-4), 5.23 (dd, $J_{2,OH}$=8.2 Hz, $J_{2,3}$=2.4 Hz, 1H, H-2), 5.08 (dd, $J_{3,4}$=8.2 Hz, $J_{2,3}$=2.4 Hz, 1H, H-3), 3.95 (dd, $J_{2',3'A}$=5.1 Hz, $J_{2',3'B}$=7.5 Hz, 1H, H-2′), 3.79 (q, $J_{5,6}$=7.4 Hz, 2H, H-5), 3.78 (q, $J_{5'',6''}$=7.1 Hz, 2H, H-5″), 3.16 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 2H, H_A-10′), 3.08 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 2H, H_B-10′), 2.15–2.03 (m, 2H, H3′), 2.20–1.83 (m, 3H, H-4′, H-6′), 1.55-1.32 (m, 2H, H-5′), 1.26 (t, $J_{5,6}$=7.1 Hz, 3H, H-6), 1.18 (t, $J_{5'',6''}$=7.4 Hz, 3H, H-6″), 0.99 (s, 3H, H-8′), 0.93 (s, 3H, H-9′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 169.8 (C-1), 99.2 (C-4), 89.4 (C-3), 69.4 (C-2), 65.2 (C-2′), 63.3 (C-5, C-5″), 52.8 (C-10′), 49.1 (C-1′), 47.9 (C-7′), 44.4 (C-4′), 37.5 (C-3′), 32.7 (C-6′), 26.4 (C-5′), 20.4 (C-8′), 19.9 (C-9′), 15.1 (C-6), 14.9 (C-6″).

4.2.9. (2′*R*)-*N*-[4,4-Diethoxy-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-bornane-10′,′2-sultam (7ab). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 5.57 (dd, $J_{2,OH}$=6.2 Hz, $J_{2,3}$=6.6 Hz, 1H, H-2), 3.50 (dd, $J_{2',3'A}$=4.6 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′); ^{13}C (125 MHz; $CDCl_3$): δ 170.6 (C-1), 99.6 (C-4), 89.6 (C-3), 71.6 (C-2), 52.2 (C-10′), 48.6 (C-1′), 47.6 (C-7′), 44.3 (C-4′), 26.0 (C-5′), 13.7 (C-6).

4.2.10. (2′*R*)-*N*-[4,4-Diethoxy-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-bornane-10′,′2-sultam (8ab). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 5.44 (dd, $J_{3,4}$=8.4 Hz, $J_{2,3}$=6.0 Hz, 1H, H-2), 3.97 (d, $J_{2,3}$=6.0 Hz, 1H, OH), 3.31 (dd, $J_{2',3'A}$=4.8 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′); ^{13}C (125 MHz; $CDCl_3$): δ 47.5 (C-7′), 44.3 (C-4′), 26.1 (C-5′).

4.2.11. (2′*R*)-*N*-[4,4-Diethoxy-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-bornane-10′,′2-sultam (9ab). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 3.82 (d, $J_{2,3}$=7.8 Hz, 1H, OH), 3.48 (dd, $J_{2',3'A}$=4.6 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′); ^{13}C (50 MHz; $CDCl_3$): δ 168.4 (C-1), 96.1 (C-4), 65.1 (C-2′), 52.0 (C-10′), 47.4 (C-7′), 44.2 (C-4′), 14.9 (C-6).

4.2.12. (2′*R*)-*N*-[(2*S*)-Hydroxy-(3*R*)-nitro-3-phenylpropanoyl]-bornane-10′,2′-sultam (6ac). Colourless crystals, mp=169–170 °C (hexane/AcOEt); HRMS-EI: Calcd for $C_{19}H_{25}N_2O_6S$ $(M+H)^+$ 409.1433, found 409.1432. Anal. Calcd for $C_{19}H_{24}N_2O_6S$: C. 55.87, H. 5.92, N. 6.86, S. 7.85, found C. 55.79, H. 6.08, N. 6.80, S. 7.87; IR (KBr): 3496, 3291, 2999, 2944, 2909, 1682, 1561, 1367, 1320, 1214, 1137, 1072, 719, 532 cm^{-1}; $[\alpha]_D{}^{20}=-68$ (c=1.39; $CHCl_3$); R_f=0.4 (hexane/AcOEt 7:3); ^1H NMR (500 MHz; $CDCl_3$): δ 7.60–7.35 (m, 5H, Ar), 5.95 (d, $J_{2,3}$=6.6 Hz, 1H, H-3), 5.55 (dd, $J_{2,3}$=6.6 Hz, $J_{2,OH}$=6.5 Hz, 1H, H-2), 3.97 (dd, $J_{2',3'A}$=4.7 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′), 3.66 (d, $J_{2,OH}$=6.5 Hz, 1H, OH), 3.51 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 3.46 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_B-10′), 1.95–1.85 (m, 4H, H-4′, H-6′), 1.78–1.74 (m, 1H, H_A-3′), 1.67–1.60 (m, 1H, H_B-3′), 1.42–1.36 (m, 1H, H_A-5′), 1.33–1.23 (m, 1H, H_B-5′), 0.92 (s, 3H, H-8′), 0.79 (s, 3H, H-9′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 168.7 (C-1), 130.3 (i-Ar),130.1 (Ar), 129.2 (Ar), 128.8 (Ar), 92.0 (C-3), 72.0 (C-2), 65.1 (C-2′), 52.9 (C-10′), 48.9 (C-1′), 47.7 (C-7′), 44.5 (C-4′), 37.4 (C-3′), 32.7 (C-6′), 26.3 (C-5′), 20.4 (C-8′), 19.7 (C-9′).

4.2.13. (2′*R*)-*N*-[*anti*-(2ξ)-Hydroxy-(3ξ)-nitro-3-phenylpropanoyl]-bornane-10′,2′-sultam (7ac). Colourless oil, ^1H NMR (500 MHz; $CDCl_3$): δ 7.46–7.38 (m, 5H, Ar), 5.93 (d, $J_{2,3}$=6.7 Hz, 1H, H-3), 5.69 (dd, $J_{2,3}$=6.7 Hz, $J_{2,OH}$=5.8 Hz, 1H, H-2), 3.93 (dd, $J_{2',3'A}$=4.8 Hz, $J_{2',3'B}$=8.2 Hz, 1H, H-2′), 3.38 (d, $J_{2,OH}$=6.5 Hz, 1H, OH), 3.61 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 3.52 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_B-10′), 2.01–1.50 (m, 6H, H-4′, H-6′, H-3′), 1.46–1.40 (m, 1H, H_A-5′), 1.38–1.31 (m, 1H, H_B-5′), 1.22 (s, 3H, H-8′), 1.01 (s, 3H, H-9′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 171.2 (C-1), 130.1 (i-Ar),130.0 (Ar), 129.1 (Ar), 128.3 (Ar), 89.2 (C-3), 70.9 (C-2), 64.2 (C-2′), 52.8 (C-10′), 49.1 (C-1′), 47.8 (C-7′), 44.6 (C-4′), 37.7 (C-3′), 32.8 (C-6′), 26.7 (C-5′), 20.8 (C-8′), 19.0 (C-9′).

4.2.14. (2′*R*)-*N*-[(2*R*)-Hydroxy-(3*S*)-nitro-3-phenylpropanoyl]-bornane-10′,2′-sultam (8ac). Colourless oil, $[\alpha]_D{}^{20}=-41$ (c=1.11; $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 7.50–7.38 (m, 5H, Ar), 5.85 (d, $J_{2,3}$=9.0 Hz, 1H, H-3), 5.49 (dd, $J_{2,3}$=9.0 Hz, $J_{2,OH}$=6.1 Hz, 1H, H-2), 3.97 (dd, $J_{2',3'A}$=4.9 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′), 3.57 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_A-10′), 3.55 (d_{AB}, $J_{10'A,10'B}$=13.8 Hz, 1H, H_B-10′), 3.51 (d, $J_{2,OH}$=6.5 Hz, 1H, OH), 2.23–2.18 (m, 1H, H_A-3′), 2.10–2.04 (m, 1H, H_B-3′), 1.99–1.85 (m, 4H, H-4′, H-6′), 1.50–1.45 (m, 1H, H_A-5′), 1.39–1.33 (m, 1H, H_B-5′), 1.12 (s, 3H, H-8′), 0.98 (s, 3H, H-9′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 168.2 (C-1), 131.5 (i-Ar),130.0 (Ar), 128.9 (Ar), 128.3 (Ar), 87.9 (C-3), 70.8 (C-2), 65.0 (C-2′), 52.6 (C-10′), 49.5 (C-1′), 47.8 (C-7′), 44.3 (C-4′), 37.4 (C-3′), 32.5 (C-6′), 26.3 (C-5′), 20.4 (C-8′), 19.7 (C-9′).

4.2.15. (2′*R*)-*N*-[(2*S*)-Hydroxy-(3*R*)-nitro-4-phenylbutanoyl]-bornane-10′,2′-sultam (6ad). Colourless oil, HRMS-ESI: Calcd for $C_{20}H_{26}N_2O_6SNa$ $(M+Na)^+$ 445.1404, found 445.1415. Anal. Calcd C. 56.86, H. 6.20, N. 6.63, S. 7.59, found C. 57.09, H. 6.31, N. 6.46, S. 7.71; IR (film): 3470, 2961, 1694, 1555, 1335, 1294, 1167, 1138, 1061, 753, 700, 535 cm^{-1}; $[\alpha]_D{}^{20}=-60$ (c=1.10; $CHCl_3$); R_f=0.4 (hexane/AcOEt 7:3); ^1H NMR (500 MHz; $CDCl_3$): δ 7.34–7.25 (m, 5H, Ar), 5.34 (ddd, $J_{2,3}$=2.2 Hz, $J_{3,4A}$=5.8 Hz, $J_{3,4B}$=9.1 Hz, 1H, H-3), 4.92 (dd, $J_{2,3}$=2.2 Hz, $J_{2,OH}$=7.1 Hz, 1H, H-2), 3.96 (dd, $J_{2',3'A}$=4.8 Hz, $J_{2',3'B}$=7.9 Hz, 1H, H-2′), 3.58 (dd_{AB}, $J_{3,4B}$=9.1 Hz, $J_{4A,4B}$=14.5 Hz, 1H, H_B-4), 3.27 (dd_{AB}, $J_{3,4A}$=5.8 Hz, $J_{4A,4B}$=14.5 Hz, 1H, H_A-4), 3.13 (d_{AB}, $J_{10'A,10'B}$=13.7 Hz, 1H, H_A-10′), 3.08 (d_{AB}, $J_{10'A,10'B}$=13.7 Hz, 1H, H_B-10′), 2.01–1.81 (m, 3H, H-3′, H-4′), 1.49–1.29 (m, 2H, H-6′), 1.20–1.08 (m, 1H, H-5′), 1.19 (s, 3H, H-8′), 0.97 (s, 3H, H-9′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3 (C-1), 134.9 (i-Ar),129.3 (Ar), 128.6 (Ar), 127.3 (Ar), 90.2 (C-3), 71.3 (C-2), 65.3 (C-2′), 52.8 (C-10′), 49.2 (C-1′), 47.9 (C-7′), 44.3 (C-4′), 37.2 (C-3′), 35.4 (C-4), 32.5 (C-6′), 26.4 (C-5′), 20.2 (C-8′), 19.8 (C-9′).

4.2.16. (2′*R*)-*N*-[(2ξ)-Hydroxy-(3ξ)-nitro-4-phenylbutanoyl]-bornane-10′,2′-sultam (7ad). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ

5.32 (dd, $J_{2,3}$=4.9 Hz, $J_{2,OH}$=5.8 Hz, 1H, H-2), 5.21 (ddd, $J_{2,3}$=4.9 Hz, $J_{3,4A}$=4.0 Hz, $J_{3,4B}$=8.8 Hz, 1H, H-3), 3.92 (dd, $J_{2',3'A}$=4.4 Hz, $J_{2',3'B}$=7.9 Hz, 1H, H-2′), 3.55 (d_{AB}, $J_{10'A,10'B}$=13.7 Hz, 1H, H_A-10′), 3.49 (d_{AB}, $J_{10'A,10'B}$=13.7 Hz, 1H, H_B-10′), 3.43 (dd_{AB}, $J_{3,4B}$=8.8 Hz, $J_{4A,4B}$=15.0 Hz, 1H, H_B-4), 3.14 (dd_{AB}, $J_{3,4A}$=4.0 Hz, $J_{4A,4B}$=15.0 Hz, 1H, H_A-4), 1.06 (s, 3H, H-8′), 0.95 (s, 3H, H-9′); ^{13}C (125 MHz; $CDCl_3$): δ 169.3 (C-1), 134.8 (i-Ar), 129.0 (Ar), 128.7 (Ar), 127.3 (Ar), 88.2 (C-3), 70.4 (C-2), 65.3 (C-2′), 52.8 (C-10′), 49.1 (C-1′), 47.8 (C-7′), 44.4 (C-4′), 37.7 (C-3′), 35.4 (C-4), 32.7 (C-6′), 26.2 (C-5′), 20.7 (C-8′), 19.7 (C-9′).

4.2.17. (2′R)-*N*-[(2ξ)-Hydroxy-(3ξ)-nitro-4-phenylbutanoyl]-bornane-10′,2′-sultam (8ad). Colourless crystals, mp=176–178 °C; ^{1}H (500 MHz; $CDCl_3$): δ 7.15–5.40 (m, 5H, Ar), 5.35 (dd, $J_{2,3}$=11.0 Hz, $J_{2,OH}$=6.0 Hz, 1H, H-2), 5.20–5.32 (m, 1H, H-3), 3.97 (dd, $J_{2',3'A}$=4.5 Hz, $J_{2',3'B}$=7.8 Hz, 1H, H-2′), 3.68 (d, J=6.0 Hz, 1H, OH), 3.61 (d_{AB}, $J_{10'A,10'B}$=13.7 Hz, 1H, H_A-10′), 3.52 (d_{AB}, $J_{10'A,10'B}$=13.7 Hz, 1H, H_B-10′), 3.49 (dd_{AB}, $J_{3,4B}$=8.5 Hz, $J_{4A,4B}$=15.0 Hz, 1H, H_B-4), 3.19 (dd_{AB}, $J_{3,4A}$=4.0 Hz, $J_{4A,4B}$=15.0 Hz, 1H, H_A-4), 1.84–2.15 (m, 5H), 1.30–1.55 (m, 2H), 1.13 (s, 3H, H-8′), 1.01 (s, 3H, H-9′); ^{13}C (125 MHz; $CDCl_3$): δ 168.2 (C-1), 134.6 (i-Ar), 128.9 (Ar), 128.8 (Ar), 127.5 (Ar), 89.4 (C-3), 70.7 (C-2), 65.3 (C-2′), 52.7 (C-10′), 49.3 (C-1′), 47.8 (C-7′), 44.6 (C-4′), 37.6 (C-3′), 35.9 (C-4), 32.6 (C-6′), 26.7 (C-5′), 20.4 (C-8′), 20.3 (C-9′).

4.2.18. (2′*R*)-*N*-[(2ξ)-Hydroxy-(3ξ)-nitro-4-phenylbutanoyl]-bornane-10′,2′-sultam (9ad). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 5.19–5.16 (m, 1H, H-3), 5.11–5.08 (m, 1H, H-2), 1.13 (s, 3H, H-8′); ^{13}C (125 MHz; $CDCl_3$): δ 171.0 (C-1), 135.0 (i-Ar), 89.5 (C-3), 70.2 (C-2), 64.9 (C-2′), 52.4 (C-10′), 49.2 (C-1′), 47.2 (C-7′), 44.6 (C-4′), 37.5 (C-3′), 35.0 (C-4), 31.1 (C-6′).

4.2.19. (2′*R*)-*N*-[(2ξ)-Hydroxy-3-carboxyethyl-(3ξ)-nitro-propanoyl]-bornane-10′,2′-sultam (6ae). Colourless oil, HRMS-LSIMS(+): Calcd for $C_{16}H_{25}N_2O_8S$ $(M+H)^+$ 405.1331, found 405.1316. Anal Calcd C. 47.52, H. 5.98, N. 6.93, S. 7.93, found C. 47.82, H. 6.16, N. 6.62, S. 7.87; IR (film): 3476, 2963, 1752, 1695, 1567, 1335, 1320, 1297, 1221, 1168, 1138, 1062, 1023, 857, 765, 536 cm^{-1}; R_f=0.6 (hexane/AcOEt 7:3); ^{1}H NMR (500 MHz; $CDCl_3$): δ 5.84 (d, $J_{2,3}$=5.2 Hz, 1H, H-3), 5.40 (d, $J_{2,3}$=$J_{2,OH}$=5.2 Hz, 1H, H-2), 4.36–4.25 (m, 2H, H-5), 4.00–3.93 (m, 1H, H-2′), 4.39–3.62 (m, 2H, H-10′), 2.19–1.84 (m, 5H, H-3′, H-4′, H-6′), 1.75–1.25 (m, 8H, H-5′, H-6), 1.15 (s, 3H, H-8′), 0.99 (s, 3H, H-9′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.6 (C-1), 161.6 (C-1), 88.7 (C-3), 69.6 (C-2), 65.1 (C-2′), 63.6 (C-5), 52.8 (C-10′), 49.3 (C-1′), 47.9 (C-7′), 44.4 (C-4′), 37.4 (C-3′), 32.6 (C-6′), 26.3 (C-5′), 20.4 (C-8′), 19.7 (C-9′) 13.7 (C-6).

4.2.20. (2′*R*)-*N*-[(2ξ)-Hydroxy-3-carboxyethyl-(3ξ)-nitropropanoyl]-bornane-10′,2′-sultam (7ae). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 5.70 (d, $J_{2,3}$=3.4 Hz, 1H, H-3), 5.51 (d, $J_{2,3}$=$J_{2,OH}$=3.4 Hz, 1H, H-2), 1.13 (s, 3H, H-8′), 0.95 (s, 3H, H-9′); ^{13}C (125 MHz; $CDCl_3$): δ 167.8 (C-1), 161.8 (C-1), 87.6 (C-3), 69.5 (C-2), 65.3 (C-2′), 63.5 (C-5), 52.7 (C-10′), 49.4 (C-1′), 48.0 (C-7′), 44.5 (C-4′), 37.2 (C-3′), 32.5 (C-6′), 26.9 (C-5′), 20.3 (C-8′), 19.6 (C-9′) 13.6 (C-6).

4.2.21. (2′*R*)-*N*-[(2ξ)-Hydroxy-3-carboxyethyl-(3ξ)-nitropropanoyl]-bornane-10′,2′-sultam (8ae). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 5.64 (d, $J_{2,3}$=8.3 Hz, 1H, H-3), 5.39 (d, $J_{2,3}$=$J_{2,OH}$=8.3 Hz, 1H, H-2), 1.12 (s, 3H, H-8′), 0.94 (s, 3H, H-9′); ^{13}C (125 MHz; $CDCl_3$): δ 167.4 (C-1), 161.8 (C-1), 87.8 (C-3), 70.0 (C-2), 65.0 (C-2′), 63.5 (C-5), 52.7 (C-10′), 49.4 (C-1′), 47.8 (C-7′), 44.3 (C-4′), 37.5 (C-3′), 32.4 (C-6′), 26.6 (C-5′), 20.3 (C-8′), 19.6 (C-9′) 13.6 (C-6).

4.2.22. (2′*R*)-*N*-[(2ξ)-Hydroxy-3-carboxyethyl-(3ξ)-nitropropanoyl]-bornane-10′,2′-sultam (9ae). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 5.60 (d, $J_{2,3}$=7.1 Hz, 1H, H-3), 5.51 (d, $J_{2,3}$=$J_{2,OH}$=7.1 Hz, 1H, H-2), 1.10 (s, 3H, H-8′), 0.90 (s, 3H, H-9′); ^{13}C (125 MHz; $CDCl_3$): δ 167.2 (C-1), 162.5 (C-1), 85.5 (C-3), 69.8 (C-2), 65.3 (C-2′), 63.3 (C-5), 52.9 (C-10′), 49.4 (C-1′), 47.6 (C-7′), 44.6 (C-4′), 37.6 (C-3′), 32.6 (C-6′), 26.7 (C-5′), 20.4 (C-8′), 19.8 (C-9′) 13.6 (C-6).

4.2.23. *O*-[(2*S*)-Hydroxy-3-nitropropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (4b). Colourless oil, HRMS-LSIMS(+): Calcd for $C_{19}H_{27}O_5NNa$ $(M+Na)^+$: 372.1786, found 372.1790. Anal Calcd C. 65.31, H. 7.79, N. 4.01, found C. 65.28, H. 8.03, N. 3.94; IR (film): 3486, 2957, 2924, 1732, 1557, 1376, 1224, 1124, 978, 766, 702 cm^{-1}; $[\alpha]_D^{20}$=−6.40 (c=1.15; $CHCl_3$); R_f=0.4 (hexane/AcOEt 8:2); ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.32–7.08 (m, 5H, Ar), 4.85 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.3 Hz, 1H, H-1′), 4.11 (dd_{AB}, $J_{3A,3B}$=14.5 Hz, $J_{2,3A}$=3.4 Hz, 1H, H_A-3), 3.83 (dd_{AB}, $J_{3A,3B}$=14.5 Hz, $J_{2,3B}$=4.3 Hz, 1H, H_B-3), 3.42 (t, $J_{2,3A}$=3.8 Hz, 1H, H-2), 2.40 (bs, 1H, OH), 2.40–2.08 (m, 1H, H-2′), 2.06–1.88 (m, 2H, H_A-6′, H_A-3′), 1.82–1.68 (m, 1H, H_A-4′), 1.62–1.38 (m, 1H, H_A-5′), 1.25–1.18 (m, 1H, H_B-3′), 1.27 (s, 3H, H-9′), 1.15 (s, 3H, H-10′), 1.10–0.90 (m, 2H, H_B-4′, H_B-6′), 0.90 (d, $J_{5',7'}$=6.5 Hz, 3H, H-7′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 169.8 (C-1), 152.4 (i-Ar), 127.9 (Ar), 125.0 (Ar), 124.9 (Ar), 77.2 (C-2), 76.1 (C-1′), 75.8 (C-3), 66.6 (C-2′), 40.5 (C-6′), 39.0 (C-8′), 34.2 (C-4′), 31.0 (C-5′), 30.8 (C-9′), 25.8 (C-3′), 21.5 (C-7′), 20.9 (C-10″).

4.2.24. *O*-[(2*R*)-Hydroxy-3-nitropropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (5b). Selected signals from differential NMR spectra: ^{1}H (200 MHz; $CDCl_3$): δ 4.93 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.9 Hz, $J_{1',6'B}$=4.5 Hz, 1H, H-1′), 4.18 (dd_{AB}, $J_{3A,3B}$=15.4 Hz, $J_{2,3A}$=5.3 Hz, 1H, H_A-3), 4.06 (dd_{AB}, $J_{3A,3B}$=15.4 Hz, $J_{2,3B}$=6.1 Hz, 1H, H_B-3), 1.30 (s, 3H, H-9′), 1.19 (s, 3H, H-10′); ^{13}C (50 MHz; $CDCl_3$): δ 169.1 (C-1), 152.3 (i-Ar), 128.0 (Ar), 127.5 (Ar), 125.0 (Ar), 77.3 (C-2), 67.9 (C-2′), 40.8 (C-6′), 39.1 (C-8′), 31.1 (C-5′), 26.0 (C-3′), 21.4 (C-7′).

4.2.25. *O*-[*syn*-(2ξ)-Hydroxy-(3ξ)-nitrooctanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (6ba). Colourless oil, HRMS-LSIMS(+): Calcd for $C_{24}H_{38}O_5N$ $(M+H)^+$: 420.2750, found 420.2745. Anal Calcd C. 68.71, H. 8.89, N. 3.34, found C. 68.71, H. 9.10, N. 3.35; IR (film): 3497, 2957, 2927, 2870, 1732, 1555, 1458, 1258, 1130, 1094, 976,

766 cm^{-1}; $[\alpha]_D{}^{20}$=26.4 (c=1.42; $CHCl_3$); R_f=0.6 (hexane/AcOEt 8:2); ^1H NMR (500 MHz; $CDCl_3$): δ 7.33–7.23 (m, 4H, Ar), 7.21–7.09 (m, 1H, Ar), 4.90 (dt, $J_{1',6'A}=J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.4 Hz, 1H, H-1′), 4.00 (ddd, $J_{2,3}$=3.0 Hz, $J_{3,4A}$=10.9 Hz, $J_{3,4B}$=6.8 Hz, 1H, H-3), 3.10 (dd, $J_{2,3}$=3.0 Hz, $J_{2,OH}$=6.5 Hz, 1H, H-2), 2.88 (d, $J_{2,OH}$=6.5 Hz, 1H, OH), 2.31–2.12 (m, 1H, H-2′), 2.10–2.00 (m, 1H, H_A-3′), 1.99–1.84 (m, 3H, H-4, H_A-6′), 1.76–1.71 (m, 3H, H-5, H_A-4′), 1.56–1.29 (m, 6H, H-6, H-7, H-3′, H_A-5′), 1.28 (s, 3H, H-9′), 1.16 (s, 3H, H-10′), 1.01–0.86 (m, 8H, H_B-4′, H_B-6′, H-7′, H-8); ^{13}C NMR (125 MHz; $CDCl_3$): δ 168.2 (C-1), 152.5 (i-Ar), 127.9 (Ar), 125.2 (Ar), 125.0 (Ar), 87.6 (C-3), 76.9 (C-1′), 71.7 (C-2), 50.1 (C-2′), 40.6 (C-6′), 39.2 (C-8′), 34.3 (C-4′), 31.0 (C-9′), 30.5 (C-5′), 30.4 (C-5), 28.3 (C-4), 26.0 (C-3′), 25.6 (C-6), 22.3 (C-7), 21.8 (C-7′), 21.7 (C-10′), 13.8 (C-8).

4.2.26. *O*-[*anti*-(2ξ)-Hydroxy-(3ξ)-nitrooctanoyl]-(1′*R*, 2′*S*,5′*R*)-8′-phenylmenthol (7ba). Colourless oil, ^1H NMR (500 MHz; $CDCl_3$): δ 4.92 (dt, $J_{1',6'A}=J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.4, 1H, H-1′), 4.19 (dt, $J_{2,3}=J_{3,4B}$=3.2 Hz, $J_{3,4A}$= 7.3 Hz, 1H, H-3), 3.72 (dd, $J_{2,3}$=3.2 Hz, $J_{2,OH}$=4.8 Hz, 1H, H-2), 2.95 (d, $J_{2,OH}$ Hz=4.8, 1H), OH, 1.24 (s, 3H, H-9′), 1.15 (s, 3H, H-10′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3 (C-1), 152.4 (i-Ar), 127.9 (Ar), 125.2 (Ar), 125.0 (Ar), 87.5 (C-3), 76.8 (C-1′), 69.6 (C-2), 50.0 (C-2′), 40.6 (C-6′), 39.1 (C-8′), 34.3 (C-4′), 31.1 (C-9′), 30.9 (C-5), 30.8 (C-5′), 28.2 (C-4), 26.0 (C-3′), 25.5 (C-6), 22.1 (C-7), 21.7 (C-7′), 21.6 (C-10′), 13.7 (C-8).

4.2.27. *O*-[(2ξ)-Hydroxy-(3ξ)-nitrooctanoyl]-(1′*R*, 2′*S*,5′*R*)-8′-phenylmenthol (8ba). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 4.97 (dt, $J_{1',6'A}=J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.5 Hz, 1H, H-1′), 4.22 (dt, $J_{2,3}=J_{3,4B}$=3.8 Hz, $J_{3,4A}$=9.9 Hz, 1H, H-3), 3.37 (dd, $J_{2,3}$= 3.8 Hz, $J_{2,OH}$=4.0 Hz, 1H, H-2), 3.03 (d, $J_{2,OH}$=4.0 Hz, 1H, OH), 1.24 (s, 3H, H-9′), 1.15 (s, 3H, H-10′); ^{13}C (125 MHz; $CDCl_3$): δ 170.3 (C-1), 151.7 (i-Ar), 128.0 (Ar), 125.1 (Ar), 125.0 (Ar), 89.2 (C-3), 77.0 (C-1′), 70.2 (C-2), 50.2 (C-2′), 41.2 (C-6′), 39.2 (C-8′), 34.2 (C-4′), 31.1 (C-9′), 30.9 (C-5′), 30.3 (C-5), 28.2 (C-4), 26.0 (C-3′), 25.5 (C-6), 22.1 (C-7), 21.7 (C-7′), 21.6 (C-10′), 13.7 (C-8).

4.2.28. *O*-[(2ξ)-Hydroxy-(3ξ)-nitrooctanoyl]-(1′*R*, 2′*S*,5′*R*)-8′-phenylmenthol (9ba). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 4.94 (dt, $J_{1',6'A}=J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.5 Hz, 1H, H-1′), 4.49 (dt, $J_{2,3}=J_{3,4B}$=4.5 Hz, $J_{3,4A}$=9.0 Hz, 1H, H-3), 1.30 (s, 3H, H-9′), 1.17 (s, 3H, H-10′); ^{13}C (125 MHz; $CDCl_3$): δ 169.5 (C-1), 152.5 (i-Ar), 87.0 (C-3), 76.6 (C-1′), 70.8 (C-2), 49.5 (C-2′), 40.9 (C-6′), 39.3 (C-8′), 34.4 (C-4′), 31.2 (C-9′), 30.4 (C-5′), 30.3 (C-5), 28.8 (C-4), 26.2 (C-3′), 25.4 (C-6), 22.1 (C-7), 21.7 (C-7′), 21.5 (C-10′), 13.8 (C-8).

4.2.29. *O*-[4,4-Diethoxy-*syn*-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (6bb). Colourless oil, HRMS-LSIMS(+): Calcd for $C_{24}H_{38}O_7N$ $(M+H)^+$: 452.2648, found 452.2643. Anal. Calcd C. 63.87, H. 8.26, N. 3.10, found C. 63.62, H. 8.45, N. 3.10; IR (film): 3492, 2961, 2926, 1737, 1556, 1445, 1327, 1278, 1120, 1066, 766, 702 cm^{-1}; $[\alpha]_D{}^{20}$=−13.5 (c=0.98; $CHCl_3$); R_f=0.5 (hexane/AcOEt 8:2); ^1H NMR (500 MHz; $CDCl_3$): δ 7.29–7.10 (m, 5H, Ar), 4.97 (d, $J_{3,4}$=8.0 Hz, 1H, H-4), 4.93 (dt, $J_{1',6'A}=J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.5 Hz, 1H, H-1′), 4.28 (dd, $J_{2,3}$=2.5 Hz, $J_{3,4}$=8.0 Hz, 1H, H-3), 3.63 (dd, $J_{5A,5B}$=9.2 Hz, $J_{5,6}$=7.1 Hz, 2H, H-5), 3.56 (dd, $J_{5''A,5''B}$=9.2 Hz, $J_{5'',6''}$=7.1 Hz, 2H, H-5″), 3.40 (dd, $J_{2,3}$= 2.5 Hz, $J_{2,OH}$=7.3 Hz, 1H, H-2), 2.91 (d, $J_{2,OH}$=7.3 Hz, 1H, OH), 2.12 (ddd, $J_{1',2'}$=10.8 Hz, $J_{2',3'A}$=12.3 Hz, $J_{2',3'B}$= 3.7 Hz, 1H, H-2′), 1.98–1.92 (m, 1H, H_A-3′), 1.89–1.84 (m, 1H, H_A-6′), 1.75–1.70 (m, 1H, H_A-4′), 1.52–1.40 (m, 1H, H_A-5′), 1.30 (s, 3H, H-9′), 1.29 (t, $J_{5,6}$=7.1 Hz, 3H, H-6), 1.20–1.14 (m, 1H, H_B-3′), 1.10–0.91 (m, 2H, H_B-4′, H_B-6′), 1.18 (s, 3H, H-10′), 1.15 (t, $J_{5'',6''}$=7.1 Hz, 3H, H-6″), 0.90 (d, $J_{5',7'}$=6.5 Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.1 (C-1), 151.7 (i-Ar), 127.9 (Ar), 125.3 (Ar), 125.2 (Ar), 99.5 (C-4), 88.5 (C-3), 76.9 (C-1′), 68.4 (C-2), 64.8 (C-5), 64.5 (C-5″), 50.3 (C-2′), 40.8 (C-6′), 39.2 (C-8′), 34.4 (C-4′), 31.3 (C-5′), 30.4 (C-9′), 26.1 (C-3′), 21.8 (C-7′), 21.7 (C-10′), 15.3 (C-6), 15.0 (C-6″).

4.2.30. *O*-[4,4-Diethoxy-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (7bb). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 5.01 (d, $J_{3,4}$=8.1 Hz, 1H, H-4), 4.41 (dd, $J_{2,3}$=1.7 Hz, $J_{3,4}$=8.1 Hz, 1H, H-3), 3.40 (dd, $J_{2,3}$=1.7 Hz, $J_{2,OH}$= 3.9 Hz, 1H, H-2); ^{13}C (125 MHz; $CDCl_3$): δ 169.5 (C-1), 151.3 (i-Ar), 128.0 (Ar), 125.5 (Ar), 125.0 (Ar), 99.3 (C-4), 88.9 (C-3), 77.0 (C-1′), 68.9 (C-2), 65.3 (C-5), 64.6 (C-5″), 50.1 (C-2′), 41.0 (C-6′), 39.4 (C-8′), 34.4 (C-4′), 31.3 (C-5′), 30.2 (C-9′), 26.1 (C-3′), 22.6 (C-7′), 21.7 (C-10′), 15.1 (C-6), 15.0 (C-6″).

4.2.31. *O*-[4,4-Diethoxy-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (8bb). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 5.01 (d, $J_{3,4}$=7.7 Hz, 1H, H-4), 4.59 (dd, $J_{2,3}$=2.2 Hz, $J_{3,4}$=7.7 Hz, 1H, H-3), 4.11 (dd, $J_{2,3}$=2.2 Hz, $J_{2,OH}$= 3.9 Hz, 1H, H-2), 3.05 (d, $J_{2,OH}$=3.9 Hz, 1H, OH); ^{13}C (125 MHz; $CDCl_3$): δ 168.8 (C-1), 152.1 (i-Ar), 127.9 (Ar), 99.2 (C-4), 87.6 (C-3), 77.0 (C-1′), 69.6 (C-2), 64.7 (C-5), 64.4 (C-5″), 49.8 (C-2′), 39.2 (C-8′), 34.4 (C-4′), 31.2 (C-5′), 29.6 (C-9′), 26.3 (C-3′), 22.8 (C-7′), 22.1 (C-10′), 15.2 (C-6), 14.1 (C-6″).

4.2.32. *O*-[4,4-Diethoxy-(2ξ)-hydroxy-(3ξ)-nitrobutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (9bb). Selected signals from differential NMR spectra: ^1H (500 MHz; $CDCl_3$): δ 5.15 (d, $J_{3,4}$=8.1 Hz, 1H, H-4), 4.73 (dd, $J_{2,3}$=2.9 Hz, $J_{3,4}$=8.1 Hz, 1H, H-3), 4.01 (dd, $J_{2,3}$=2.9 Hz, $J_{2,OH}$= 2.3 Hz, 1H, H-2); ^{13}C (125 MHz; $CDCl_3$): δ 167.9 (C-1), 152.9 (i-Ar), 128.0 (Ar), 89.2 (C-3), 77.2 (C-1′), 70.2 (C-2), 66.7 (C-5), 64.1 (C-5″), 49.8 (C-2′), 39.4 (C-8′), 34.4 (C-4′), 30.9 (C-5′), 29.8 (C-9′), 26.3 (C-3′), 22.5 (C-7′), 22.2 (C-10′).

4.2.33. *O*-[(2*S*)-Hydroxy-(3*R*)-nitro-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (6bc). Colourless crystals, mp=179–180 °C (hexane/AcOEt); HRMS-LSIMS (+): Calcd for $C_{25}H_{31}O_5NNa$ $(M+Na)^+$ 448.2099, found 448.2087. Anal. Calcd C. 70.57, H. 7.34, N. 3.29, found C. 70.10, H. 7.55, N. 3.32; IR (KBr): 3479 2958, 2924, 1730, 1556, 1496, 1456, 1366, 1258, 1121, 957, 766, 701 cm^{-1}; $[\alpha]_D{}^{20}$=7.2 (c=0.93; $CHCl_3$); R_f=0.5 (hexane/AcOEt 8:2)^1H NMR (500 MHz; $CDCl_3$): δ 7.50–7.06 (m, 10H, 2xAr), 5.14 (d, $J_{2,3}$=5.1 Hz, 1H, H-3), 4.87 (dt,

$J_{1',6'A}=J_{1',2'}=10.8$ Hz, $J_{1',6'B}=4.5$ Hz, 1H, H-1′), 3.63 (dd, $J_{2,3}=5.1$ Hz, $J_{2,OH}=6.1$ Hz, 1H, H-2), 3.05 (d, $J_{2,OH}=6.1$ Hz, 1H, OH), 2.07 (ddd, $J_{1',2'}=10.8$ Hz, $J_{2',3'A}=3.6$ Hz, $J_{2',3'B}=12.1$ Hz, 1H, H-2′), 1.99 (dd, $J_{2',3'A}=J_{4'A,3'A}=3.6$ Hz, $J_{3'A,3'B}=13.5$ Hz, 1H, H_A-3′), 1.78–1.71 (m, 1H, H_A-6′), 1.67–1.62 (m, 1H, H_A-4′), 1.52–1.41 (m, 1H, H_A-5′), 1.30 (s, 3H, H-9′), 1.26–1.19 (m, 1H, H_B-3′), 1.15 (s, 3H, H-10′), 1.00–0.89 (m, 2H, H_B-4′, H_B-6′), 0.87 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 169.9 (C-1), 152.3 (i-Ar), 131.0 (i-Ar), 129.9 (Ar), 129.1 (Ar), 128.6 (Ar), 127.9 (Ar), 125.4 (Ar), 124.2 (Ar), 91.1 (C-3), 76.9 (C-1′), 71.1 (C-2), 50.1 (C-2′), 40.5 (C-6′), 39.1 (C-8′), 34.2 (C-4′), 31.1 (C-5′), 30.8 (C-9′), 25.9 (C-3′), 21.6 (C-7′), 21.3 (C-10′).

4.2.34. *O*-[*anti*-(2ξ)-Hydroxy-(3ξ)-nitro-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (7bc). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 5.25 (d, $J_{2,3}=4.5$ Hz, 1H, H-3), 4.94 (dt, $J_{1',6'A}=J_{1',2'}=10.8$ Hz, $J_{1',6'B}=4.2$ Hz, 1H, H-1′), 4.21 (dd, $J_{2,3}=4.5$ Hz, $J_{2,OH}=4.8$ Hz, 1H, H-2), 3.05 (d, $J_{2,OH}=4.8$ Hz, 1H, OH), 1.34 (s, 3H, H-9′), 1.20 (s, 3H, H-10′), 0.86 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′); ^{13}C (125 MHz; $CDCl_3$): δ 169.7 (C-1), 152.0 (i-Ar), 131.3 (i-Ar), 129.9 (Ar), 129.8 (Ar), 128.3 (Ar), 128.2 (Ar), 125.3 (Ar), 125.0 (Ar), 89.6 (C-3), 77.5 (C-1′), 70.5 (C-2), 50.3 (C-2′), 40.9 (C-6′), 39.3 (C-8′), 34.4 (C-4′), 31.2 (C-5′), 30.4 (C-9′), 26.0 (C-3′), 21.6 (C-7′), 21.5 (C-10′).

4.2.35. *O*-[(2ξ)-Hydroxy-(3ξ)-nitro-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (8bc). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 5.39 (d, $J_{2,3}=5.2$ Hz, 1H, H-3), 4.73 (dt, $J_{1',6'A}=J_{1',2'}=10.8$ Hz, $J_{1',6'B}=4.4$ Hz, 1H, H-1′), 4.60 (dd, $J_{2,3}=5.1$ Hz, $J_{2,OH}=3.8$ Hz, 1H, H-2), 2.95 (d, $J_{2,OH}=3.8$ Hz, 1H, OH), 1.25 (s, 3H, H-9′), 1.15 (s, 3H, H-10′), 0.78 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′); ^{13}C (125 MHz; $CDCl_3$): δ 168.7 (C-1), 152.5 (i-Ar), 129.8 (Ar), 129.2(Ar), 128.0 (Ar), 125.4 (Ar), 125.0 (Ar), 89.5 (C-3), 77.4 (C-1′), 72.3 (C-2), 49.8 (C-2′), 40.8 (C-6′), 39.2 (C-8′), 34.2 (C-4′), 31.1 (C-5′), 30.2 (C-9′), 26.3 (C-3′), 22.3 (C-7′), 21.0 (C-10′).

4.2.36. *O*-[(2*S*)-Hydroxy-(3*R*)-nitro-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (6bd). Colourless crystals, mp=85 °C (hexane/Et2O); HRMS-ESI: Calcd for $C_{26}H_{33}O_5NNa$ $(M+Na)^+$ 462.2251, found 462.2251. Anal. Calcd C. 71.05, H. 7.57, N. 3.19, found C. 70.90, H. 7.61, N. 3.03; IR (KBr): 3567, 2960, 2920, 1718, 1546, 1367, 1282, 1126, 986, 758, 695, 491 cm^{-1}; $[\alpha]_D{}^{20}=26$ (c=1.11; $CHCl_3$); R_f=0.5 (hexane/AcOEt 8:2); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.40–7.30 (m, 3H, Ar), 7.22–7.19 (m, 4H, Ar), 7.07–7.02 (m, 2H, Ar), 6.75–6.71 (m, 1H, Ar), 4.92 (dt, $J_{1',6'A}=J_{1',2'}=10.8$ Hz, $J_{1',6'B}=4.5$ Hz, 1H, H-1′), 4.35 (ddd, $J_{2,3}=2.7$ Hz, $J_{3,4A}=6.9$ Hz, $J_{3,4B}=8.5$ Hz, 1H, H-3), 4.31 (dd_{AB}, $J_{4A,4B}=13.9$ Hz, $J_{3,4A}=6.9$ Hz, 1H, H_A-4), 3.07 (dd_{AB}, $J_{4A,4B}=13.9$ Hz, $J_{3,4B}=6.9$ Hz, 1H, H_B-4), 3.01 (dd, $J_{2,3}=2.7$ Hz, $J_{2,OH}=6.9$ Hz, 1H, H-2), 2.95 (d, $J_{2,OH}=6.9$ Hz, 1H, OH), 2.10 (ddd, $J_{1',2'}=10.6$ Hz, $J_{2',3'A}=12.1$ Hz, $J_{2',3'B}=3.7$ Hz, 1H, H-2′), 1.96 (dq, $J_{3'A,3'B}=13.5$ Hz, $J_{2',3'B}=J_{3',4'A}=3.7$ Hz, 1H, H_A-3′), 1.87–1.84 (m, 1H, H_A-6′), 1.75–1.70 (m, 1H, H_A-4′), 1.52–1.41 (m, 1H, H_A-5′), 1.23–1.16 (m, 1H, H_B-3′), 1.24 (s, 3H, H-9′), 1.12 (s, 3H, H-10′), 1.00–0.90 (m, 2H, H_B-4′, H_B-6′), 0.89 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.3 (C-1), 151.8 (i-Ar), 135.0 (i-Ar), 129.3 (Ar), 128.8 (Ar), 127.6 (Ar), 127.4 (Ar), 125.1 (Ar), 125.0 (Ar), 88.5 (C-3), 76.9 (C-1′), 68.7 (C-2), 50.1 (C-2′), 40.7 (C-6′), 39.1 (C-8′), 35.4 (C-4), 34.4 (C-4′), 31.2 (C-5′), 30.6 (C-9′), 26.0 (C-3′), 21.6 (C-7′), 21.3 (C-10′).

4.2.37. *O*-[(2*S*)-Hydroxy-(3*S*)-nitro-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (7bd). Colourless crystals, mp=91–93 °C (hexane/AcOEt); $[\alpha]_D{}^{20}=-21$ (c=1.27; $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.31–7.21 (m, 7H, Ar), 7.16–7.12 (m, 1H, Ar), 7.08–7.025 (m, 2H, Ar), 4.94 (dt, $J_{1',6'A}=J_{1',2'}=10.8$ Hz, $J_{1',6'B}=4.4$ Hz, 1H, H-1′), 4.46 (ddd, $J_{2,3}=3.9$ Hz, $J_{3,4A}=9.7$ Hz, $J_{3,4B}=4.5$ Hz, 1H, H-3), 3.47 (dd, $J_{2,3}=3.9$ Hz, $J_{2,OH}=4.6$ Hz, 1H, H-2), 3.19 (dd_{AB}, $J_{4A,4B}=14.9$ Hz, $J_{3,4A}=9.7$ Hz, 1H, H_A-4), 3.01 (d, $J_{2,OH}=4.6$ Hz, 1H, OH), 2.73 (dd_{AB}, $J_{4A,4B}=14.9$ Hz, $J_{3,4B}=4.5$ Hz, 1H, H_B-4), 2.16 (ddd, $J_{1',2'}=10.8$ Hz, $J_{2',3'A}=12.2$ Hz, $J_{2',3'B}=3.6$ Hz, 1H, H-2′), 1.96 (dq, $J_{3'A,3'B}=13.5$ Hz, $J_{2',3'B}=J_{3',4'A}=3.6$ Hz, 1H, H_A-3′), 1.80–1.71 (m, 1H, H_A-6′, H_A-4′), 1.53–1.41 (m, 1H, H_A-5′), 1.23–1.16 (m, 1H, H_B-3′), 1.29 (s, 3H, H-9′), 1.18 (s, 3H, H-10′), 1.10–0.91 (m, 2H, H_B-4′, H_B-6′), 0.90 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.0 (C-1), 151.7 (i-Ar), 135.4 (i-Ar), 128.9 (Ar), 128.7 (Ar), 128.1 (Ar), 127.4 (Ar), 125.4 (Ar), 125.1 (Ar), 90.2 (C-3), 77.4 (C-1′), 70.2 (C-2), 50.2 (C-2′), 41.2 (C-6′), 39.3 (C-8′), 34.3 (C-4), 34.2 (C-4′), 31.3 (C-5′), 30.4 (C-9′), 26.1 (C-3′), 21.8 (C-7′), 21.6 (C-10′).

4.2.38. *O*-[(2ξ)-Hydroxy-(3ξ)-nitro-4-phenylbutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (8bd). Colourless crystals, mp=126–127 °C; $[\alpha]_D{}^{20}=13$ (c=0.92; $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.39–7.35 (m, 2H, Ar), 7.33–7.29 (m, 1H, Ar), 7.26–7.24 (m, 3H, Ar), 7.20–7.13 (m, 4H, Ar), 4.90 (dt, $J_{1',6'A}=J_{1',2'}=10.8$ Hz, $J_{1',6'B}=4.4$ Hz, 1H, H-1′), 4.52 (ddd, $J_{2,3}=2.33$ Hz, $J_{3,4A}=5.8$ Hz, $J_{3,4B}=10.3$ Hz, 1H, H-3), 3.45 (dd, $J_{2,3}=2.3$ Hz, $J_{2,OH}=4.4$ Hz, 1H, H-2), 3.43 (dd_{AB}, $J_{4A,4B}=13.6$ Hz, $J_{3,4A}=5.8$ Hz, 1H, H_A-4), 3.12 (dd_{AB}, $J_{4A,4B}=13.6$ Hz, $J_{3,4B}=10.3$ Hz, 1H, H_B-4), 2.21 (ddd, $J_{1',2'}=10.7$ Hz, $J_{2',3'A}=12.2$ Hz, $J_{2',3'B}=3.6$ Hz, 1H, H-2′), 1.96 (dq, $J_{3'A,3'B}=13.5$ Hz, $J_{2',3'B}=J_{3',4'A}=3.6$ Hz, 1H, H-3′), 1.94–1.90 (m, 1H, H_A-6′), 1.75–1.71 (m, 1H, H_A-4′), 1.53–1.44 (m, 1H, H_A-5′), 1.25–1.16 (m, 1H, H_B-3′), 1.26 (s, 3H, H-9′), 1.14 (s, 3H, H-10′), 1.05–0.90 (m, 2H, H_B-4′, H_B-6′), 0.89 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 169.6 (C-1), 152.5 (i-Ar), 135.5 (i-Ar), 129.3 (Ar), 128.9 (Ar), 127.9 (Ar), 127.4 (Ar), 125.2 (Ar), 125.2 (Ar), 87.2 (C-3), 76.8 (C-1′), 69.2 (C-2), 49.7 (C-2′), 40.8 (C-6′), 39.3 (C-8′), 34.6 (C-4), 34.4 (C-4′), 31.3 (C-5′), 30.7 (C-9′), 26.2 (C-3′), 21.6 (C-7′), 21.5 (C-10′).

4.2.39. *O*-[(2ξ)-Hydroxy-3-carboxyethyl-(3ξ)-nitropropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (6be). Colourless oil, HRMS-ESI: Calcd for $C_{22}H_{31}O_7NNa$ $(M+Na)^+$: 444.1993, found 444.1960. Anal. Calcd C. 62.69, H. 7.41, N. 3.32, found C. 62.77, H. 7.41, N. 3.37; 3493, 2961, 2927, 2871, 1754, 1567, 1496, IR (film): 1444, 1368, 1257, 1199, 1129, 1029, 767, 703, 532 cm^{-1}; R_f=0.5 (hexane/AcOEt 8:2); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.35–7.25 (m, 4H, Ar), 7.17–7.08 (m, 1H, Ar), 4.94 (dt, $J_{1',6'A}=J_{1',2'}=10.7$ Hz, $J_{1',6'B}=4.5$ Hz, 1H, H-1′), 4.84 (d, $J_{2,3}=2.6$ Hz, 1H, H-3), 4.35–4.16 (m, 2H, H-5), 3.79 (dd, $J_{2,3}=2.6$ Hz, $J_{2,OH}=5.0$ Hz,

1H, H-2), 3.19 (d, $J_{2,OH}$=5.2 Hz, 1H, OH), 2.20–2.07 (m, 1H, H-2′), 2.02–1.94 (m, 1H, H_A-3′), 1.86–1.77 (m, 1H, H_A-6′), 1.77–1.71 (m, 1H, H_A-4′), 1.56–1.44 (m, 1H, H_A-5′), 1.37–1.18 (m, 1H, H_B-3′), 1.19 (s, 3H, H-9′), 1.18 (s, 3H, H-10′), 1.00–0.89 (m, 3H, H_B-4′, H_B-6′, H-6), 0.88 (d, $J_{5',7'}$=6.6 Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 168.4 (C-1), 161.6 (C-4), 151.8 (i-Ar), 128.0 (Ar), 125.5 (Ar), 125.4 (Ar), 88.2 (C-3), 77.5 (C-1′), 68.4 (C-2), 63.2 (C-5), 50.3 (C-2′), 40.8 (C-6′), 39.1 (C-8′), 34.3 (C-4′), 31.1 (C-5′), 30.3 (C-9′), 25.9 (C-3′), 21.5 (C-7′), 21.5 (C-10′), 13.7 (C-6).

4.2.40. *O*-[(2ξ)-Hydroxy-3-carboxyethyl-(3ξ)-nitropropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (7be). Selected signals from differential NMR spectra: ^{1}H (500 MHz; $CDCl_3$): δ 4.88 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.3 Hz, 1H, H-1′), 4.45 (d, $J_{2,3}$=3.4 Hz, 1H, H-3), 3.70 (dd, $J_{2,3}$=3.4 Hz, $J_{2,OH}$=7.8 Hz, 1H, H-2), 3.11 (d, $J_{2,OH}$=7.8 Hz, 1H, OH), 1.18 (s, 3H, H-9′), 1.15 (s, 3H, H-10′), 0.90 (d, $J_{5',7'}$=6.6, 3H, H-7′); ^{13}C (125 MHz; $CDCl_3$): δ 168.2 (C-1), 161.8 (C-4), 152.6 (i-Ar), 128.0 (Ar), 125.4 (Ar), 125.2 (Ar), 87.7 (C-3), 77.4 (C-1′), 68.6 (C-2), 63.2 (C-5), 50.0 (C-2′), 40.2 (C-6′), 39.0 (C-8′), 34.3 (C-4′), 31.0 (C-5′), 30.4 (C-9′), 25.8 (C-3′), 21.6 (C-7′), 21.6 (C-10′), 13.8 (C-6).

4.3. General procedure for the synthesis of nitrodiols

To a precooled solution (0 °C) of nitroalcohol (1 mmol) in THF (1 mL), $NaBH_4$ (1.1 mmol) was portionwise added. Progress of the reaction was monitored by TLC, and when finished, it was quenched by addition of saturated aqueous NaCl and extracted with AcOEt. The combined organic extracts were dried over $MgSO_4$ and evaporated. All products were purified by column chromatography (hexane/AcOEt 8:2–4:6).

4.3.1. 3-Nitropropane-(1,2*S*)-diol (10). The title compound was obtained in 85% yield from 4a, and 87% from 4b: colourless oil, HRMS-ESI: Calcd for $C_3H_8NO_4$ $(M+H)^+$ 122.1005; found 122.1008. Anal. Calcd C. 29.75, H. 5.82, N. 11.56, found C. 29.60, H. 5.92, N. 11.31; IR (film): 3366, 1552, 1384, 1111, 1048, 875 cm^{-1}; $[\alpha]_D{}^{20}$=−6.7 (*c*=0.99; $CHCl_3$); R_f=0.1 (hexane/AcOEt 1:1); ^{1}H NMR (500 MHz; D_2O): δ 4.75 (dd_{AB}, $J_{2,3A}$=3.2 Hz, $J_{3A,3B}$=13.0 Hz, 1H, H_A-3), 4.59 (dd_{AB}, $J_{2,3B}$=9.0 Hz, $J_{3A,3B}$=13.0 Hz, 1H, H_B-3), 4.43 (dddd, $J_{2,3A}$=3.2 Hz, $J_{2,3B}$=9.0 Hz, $J_{2,1A}$=5.0 Hz, $J_{2,1B}$=5.6 Hz, 1H, H-2), 3.69 (dd_{AB}, $J_{2,1A}$=5.0 Hz, $J_{1A,1B}$=11.9 Hz, 1H, H_A-1), 3.65 (dd_{AB}, $J_{2,1B}$=5.6 Hz, $J_{1A,1B}$=11.9 Hz, 1H, H_B-1); ^{13}C NMR (125 MHz; $CDCl_3$): δ 77.7 (C-3), 68.8 (C-2), 63.4 (C-1).

4.3.2. (3*R*)-Nitrooctane-(1,2*S*)-diol (11a). The title compound was obtained with 88% yield; colourless oil, HRMS-ESI: Calcd for $C_8H_{17}NO_4Na$ $(M+Na)^+$: 214.1050, found 214.1054. Anal. Calcd C. 50.25, H. 8.96, N. 7.32, found C. 50.03, H. 8.83, N. 7.20; IR (film): 3371, 2958, 2931, 2863, 1554, 1464, 1377, 1099, 1039, 833 cm^{-1}; R_f=0.2 (hexane/AcOEt 1:1); $[\alpha]_D{}^{20}$=10.5 (*c*=1.74; MeOH); ^{1}H NMR (200 MHz; $CDCl_3$): δ 4.64 (ddd, $J_{2,3}$=8.3 Hz, $J_{3,4A}$=3.9 Hz, $J_{3,4B}$=10.4 Hz, 1H, H-3), 4.15 (dd, $J_{2,3}$=8.3 Hz, $J_{2,1A}$=3.0 Hz, $J_{2,1B}$=5.5 Hz, 1H, H-2), 3.79 (dd_{AB}, $J_{2,1A}$=3.0 Hz, $J_{1A,1B}$=11.9 Hz, 1H, H_A-1), 3.61 (dd_{AB}, $J_{2,1B}$=5.5 Hz, $J_{1A,1B}$=11.9 Hz, 1H, H_B-1), 2.10–1.87 (m, 1H, H_A-4), 1.83–1.63 (m, 1H, H_B-4), 1.50–1.10 (m, 6H, H-5, H-6, H-7), 0.88–082 (m, 3H, H-8); ^{13}C NMR (50 MHz; $CDCl_3$): δ 90.3 (C-3), 72.5 (C-2), 62.9 (C-1), 30.9 (C-4), 29.9 (C-5), 25.2 (C-6), 22.2 (C-7), 13.8 (C-8).

4.3.3. *anti*-(3ξ)-Nitrooctane-(1,2ξ)-diol (11b). The title compound was obtained with 85% yield; colourless oil, HRMS-ESI: Calcd for $C_8H_{17}NO_4Na$ $(M+Na)^+$: 214.1050, found 214.1052. Anal. Calcd C. 50.25, H. 8.96, N. 7.32, found C. 50.10, H. 8.89, N. 7.19; IR (film): 3370, 2958, 2932, 2865, 1552, 1464, 1378, 1098, 1038, 834 cm^{-1}; $[\alpha]_D{}^{20}$=−21.0 (*c*=1.70; MeOH); ^{1}H NMR (200 MHz; $CDCl_3$): δ 4.63 (ddd, $J_{2,3}$=5.8 Hz, $J_{3,4A}$=3.5 Hz, $J_{3,4B}$=10.3 Hz, 1H, H-3), 4.09 (dd, $J_{2,3}$=$J_{2,1A}$=5.8 Hz, $J_{2,1B}$=3.8 Hz, 1H, H-2), 3.76 (dd_{AB}, $J_{2,1B}$=3.8 Hz, $J_{1A,1B}$=11.7 Hz, 1H, H_B-1), 3.66 (dd_{AB}, $J_{2,1A}$=5.8 Hz, $J_{1A,1B}$=11.7 Hz, 1H, H_A-1), 2.30–1.80 (m, 21H, H-4), 1.60–1.30 (m, 6H, H-5, H-6, H-7), 0.99–082 (m, 3H, H-8); ^{13}C NMR (50 MHz; $CDCl_3$): δ 89.4 (C-3), 72.2 (C-2), 62.7 (C-1), 31.0 (C-4), 29.0 (C-5), 25.4 (C-6), 22.2 (C-7), 13.8 (C-8).

4.3.4. (3*R*)-Nitro-3-phenylpropane-(1,2*S*)-diol (12a). The title compound was obtained with 90% yield. Colourless crystals, mp=83 °C (hexane/AcOEt); HRMS-ESI: Calcd for $C_9H_{11}NO_4$ $(M+Na)^+$ 220.0580; found 220.0572. Anal. Calcd C. 54.82, H. 5.62, N. 7.10, found C. 55.00, H. 5.78, N. 7.21; IR (KBr): 3541, 3400, 2928, 1649, 1539, 1370, 1320, 1100, 1049, 903, 732, 692, 632, 497 cm^{-1}; $[\alpha]_D{}^{20}$=−11.1 (*c*=0.51; ^{i}PrOH); R_f=0.2 (hexane/AcOEt 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.60–7.35 (m, 5H, Ar), 5.60 (d, $J_{2,3}$=9.9 Hz, 1H, H-3), 4.64 (ddd, $J_{2,3}$=9.9 Hz, $J_{2,1A}$=2.9 Hz, $J_{2,1B}$=4.6 Hz, 1H, H-2), 3.73 (bs, 1H, OH-2), 3.56 (dd_{AB}, $J_{2,1A}$=2.9 Hz, $J_{1A,1B}$=11.7 Hz, 1H, H_A-1), 3.29 (dd_{AB}, $J_{2,1B}$=4.6 Hz, $J_{1A,1B}$=11.7 Hz, 1H, H_B-1), 2.79 (bs, 1H, OH-1); ^{13}C NMR (125 MHz; $CDCl_3$): δ 131.2 (i-Ar),130.4 (Ar), 129.3 (Ar), 128.0 (Ar), 93.3 (C-3), 72.9 (C-2), 62.1 (C-1).

4.3.5. *anti*-(3ξ)-Nitro-3-phenylpropane-(1,2ξ)-diol (12b). The title compound was obtained with 87% yield. Colourless oil, $[\alpha]_D{}^{20}$=−8.8 (*c*=0.70; ^{i}PrOH); R_f=0.2 (hexane/AcOEt 1:1); ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.55–7.40 (m, 5H, Ar), 5.61 (d, $J_{2,3}$=7.1 Hz, 1H, H-3), 4.65 (m, 1H, H-2), 3.77 (dd_{AB}, $J_{2,1A}$=3.8 Hz, $J_{1A,1B}$=11.5 Hz, 1H, H_A-1), 3.68 (dd_{AB}, $J_{2,1B}$=4.9 Hz, $J_{1A,1B}$=11.5 Hz, 1H, H_B-1); ^{13}C NMR (125 MHz; $CDCl_3$): δ 131.2 (i-Ar),130.4 (Ar), 129.3 (Ar), 128.0 (Ar), 93.3 (C-3), 72.9 (C-2), 62.1 (C-1).

4.3.6. (3*S*)-Nitro-3-phenylpropane-(1,2*R*)-diol (12c). The title compound was obtained in 86% yield. Colourless crystals, mp=82–84 °C (hexane/AcOEt); R_f=0.2 (hexane/AcOEt 1:1); $[\alpha]_D{}^{20}$=12.0 (*c*=0.63; ^{i}PrOH).

4.3.7. *O*-[(2*S*)-*t*-Butyldimethylsilyloxy-3-nitropropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (4c). To a solution of nitroalcohol 4b (797 mg, 2.27 mmol) in DMF (3 mL) TBDMSCl (375 mg, 2.49 mmol) and imidazole were added (617 mg, 9.08 mmol). The progress of reaction was monitored by TLC. After stirring at rt for 17 h, solvents were evaporated and purification was achieved on silica-gel column using hexane/AcOEt to give compound 4c (970 mg, 92%), (R_f=0.8 hexane/AcOEt 8:2). Colourless oil, HRMS-LSIMS(+): Calcd for $C_{25}H_{45}O_5SiNNa$ $(M+Na)^+$ 486.2651, found 486.2677. Anal. Calcd C. 64.62, H. 9.11,

N. 3.01, found C. 64.76, H. 9.17, N. 2.88; IR (film): 2956, 2929, 2857, 1752, 1562, 1472, 1379, 1254, 1207, 1154, 969, 838, 766, 782, 701 cm^{-1}; $[\alpha]_D{}^{20}=-3.0$ (c=1.11; $CHCl_3$); ^1H NMR (200 MHz; $CDCl_3$): δ 7.40–7.05 (m, 5H, Ar), 4.92 (dt, $J_{1,6A}=J_{1,2}=10.8$ Hz, $J_{1,6B}=4.5$ Hz, 1H, H-1′), 4.18 (dd_{AB}, $J_{3A,3B}=14.5$ Hz, $J_{2,3A}=10.8$ Hz, 1H, H_A-3), 3.42 (dd, $J_{2,3A}=10.8$ Hz, $J_{2,3B}=7.2$ Hz, 1H, H-2), 4.15 (dd_{AB}, $J_{3A,3B}=14.5$ Hz, $J_{2,3B}=7.2$ Hz, 1H, H_B-3), 2.12–2.05 (m, 1H, H-2′), 2.02–1.80 (m, 2H, H_A-6′, H_A-3′), 1.74–1.59 (m, 2H, H_A-4′, H_A-5′), 1.35–1.22 (m, 1H, H_B-3′), 1.32 (s, 3H, H-9′), 1.24 (s, 3H, H-10′), 1.15–1.07 (m, 2H, H_B-4′, H_B-6′), 0.89 (s, 9H, $(CH_3)_3$), 0.86 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′), 0.08 (s, 6H, 2xCH_3); ^{13}C NMR (50 MHz; $CDCl_3$): δ 156.8 (C-1), 150.5 (i-Ar), 128.4 (Ar), 127.9 (Ar), 125.7 (Ar), 77.5 (C-1′), 72.9 (C-2), 62.9 (C-3), 50.2 (C-2′), 40.9 (C-6′), 39.7 (C-8′), 34.2 (C-4′), 31.3 (C-5′), 27.4 (C-9′), 26.5 (C-3′), 25.6 (3xCH_3), 21.9 (C-7′), 21.6 (C-10′), 17.9 ($C(CH_3)_3$), −3.6 (2xCH_3).

4.3.8. *O*-[3-Amino-(2*S*)-*t*-butyldimethylsilyloxy-propanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (13). Through a solution of 2-nitroalcohol 4c (227 mg, 0.49 mmol) in MeOH (5 mL) in the presence of catalytic amounts of Raney Ni, hydrogen was bubled. Progress of the reaction was monitored by TLC. After stirring at rt for 24 h, catalyst was separated, solvents evaporated and purification was achieved on silica-gel column using hexane/AcOEt to give compound 13 (206 mg, 91%). Colourless oil, (R_f=0.1 hexane/AcOEt 8:2). Colourless oil, HRMS-ESI: Calcd for $C_{25}H_{44}O_5SiN$ $(M+H)^+$ 434.3085, found 434.3093. Anal. Calcd C. 69.07, H. 10.20, N. 3.22, found C. 69.06, H. 10.09, N. 3.24; IR (film): 3392, 2954, 2928, 2857, 1745, 1600, 1496, 1471, 1389, 1363, 1252, 1172, 1134, 1082, 985, 915, 837, 779, 700 cm^{-1}; $[\alpha]_D{}^{20}=-28.0$ (c=1.31; $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$): δ 7.25–7.20 (m, 4H, Ar), 7.16–7.11 (m, 4H, Ar), 4.76 (dt, $J_{1,6A}=J_{1,2}=10.7$ Hz, $J_{1,6B}=4.3$ Hz, 1H, H-1′), 3.44 (dd, $J_{2,3B}=5.1$ Hz, $J_{2,3A}=3.9$ Hz, 1H, H-2), 2.58 (dd_{AB}, $J_{3A,3B}=13.4$ Hz, $J_{2,3A}=3.9$ Hz, 1H, H_A-3), 2.53 (dd_{AB}, $J_{3A,3B}=13.4$ Hz, $J_{2,3B}=5.1$ Hz, 1H, H_B-3), 2.11–2.04 (m, 1H, H-2′), 2.00–1.91 (m, 1H, H_A-3′), 1.75–1.60 (m, 3H, H_B-3′, H_A-4′, H_A-6′,), 1.56–1.41 (m, 1H, H_A-5′), 1.29 (s, 3H, H-9′), 1.19 (s, 3H, H-10′), 1.16–1.07 (m, 2H, H_B-4′, H_B-6′), 0.92 (s, 9H, $(CH_3)_3$), 0.86 (d, $J_{5',7'}=6.5$ Hz, 3H, H-7′), 0.12 (s, 3H, CH_3), 0.05 (s, 3H, CH_3); ^{13}C NMR (50 MHz; $CDCl_3$): δ 171.5 (C-1), 151.9 (i-Ar), 127.8 (Ar), 125.1 (Ar), 124.8 (Ar), 75.3 (C-1′), 73.6 (C-2), 50.0 (C-2′), 46.6 (C-3), 41.4 (C-6′), 39.4 (C-10′), 34.4 (C-4′), 31.1 (C-5′), 28.9 (C-9′), 26.4 (C-3′), 25.6 (3xCH_3), 24.5 (C-7′), 21.6 (C-10′), 18.2 ($C(CH_3)_3$), −4.6 (CH_3), −5.3 (CH_3).

4.3.9. 3-Amino-(2*S*)-hydroxypropionic acid ((−)-isoserin) (14). The solution of ester 13 (150 mg, 0.35 mmol) in 6N HCl aq. (5 mL) was heated at 80 °C. Progress of the reaction was monitored by TLC, and when finished (24 h) acid was removed under reduced pressure. To the residue, dry EtOH (2 mL) and epoxypropane (49 μL, 0.7 mmol) were added. The compound 14 spontaneously precipitated from the reaction mixture (49 mg, 89%). Colourless crystals, mp=187–189 °C (MeOH/H_2O); LRMS-ESI: found for $(M+Na)^+$ 128.0; $[\alpha]_D{}^{20}=-32.0$ (c=0.52; H_2O); ^1H NMR (400 MHz; H_2O): δ 4.27–4.21 (m, 1H, H-2), 3.36 (dd_{AB}, $J_{3A,3B}=12.6$ Hz, $J_{2,3A}=2.8$ Hz, 1H, H_A-3), 3.14 (dd_{AB}, $J_{3A,3B}=12.6$ Hz, $J_{2,3B}=5.1$ Hz, 1H, H_B-3); ^{13}C NMR (50 MHz; $CDCl_3$): δ 177.3 (C-1), 68.7 (C-2), 42.8 (C-3).

4.3.10. General procedure for the synthesis of *N*-Boc-aminoalcohols. Through a solution of a nitroalcohol (0.39 mmol) in MeOH (5 mL) H_2 was bubbled in the presence of catalytic amounts of Raney Ni. Progress of the reaction was monitored by TLC, and when finished, the catalyst was filtered off, solvents were evaporated and the residue was redissolved in a mixture of AcOEt and saturated aq. $NaHCO_3$ (10 mL, 1:1), followed by addition of $(Boc)_2O$ (0.43 mmol). After 2h stirring the layers were separated, and water phase was extracted with CH_2Cl_2. After drying of combined organic layers ($MgSO_4$), solvents were removed under reduced pressure. Purification was achieved on silica gel using hexane/AcOEt (9:1–7:3).

4.3.11. *O*-[*syn*-(3ξ)-*t*-Butoxycarbonylamino-(2ξ)-hydroxyoctanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (15a). The title compound was obtained in 90% yield: colourless oil, HRMS-ESI: Calcd for $C_{29}H_{48}O_5N$ $(M+H)^+$: 490.3527, found 490.3542; IR (film): 3449, 2957, 2928, 2870, 1718, 1498, 1456, 1366, 1243, 1172, 764, 700 cm^{-1}; R_f=0.55 (hexane/AcOEt 7:3); $[\alpha]_D{}^{20}=-13.0$ (c=0.48; $CHCl_3$); ^1H NMR (200 MHz; $CDCl_3$): δ 7.33–7.20 (m, 5H, Ar), 4.85 (dt, $J_{1',6'A}=J_{1',2'}=10.6$ Hz, $J_{1',6'B}=4.2$ Hz, 1H, H-1′), 4.78 (d, $J_{2,3}=10.4$ Hz, 1H, H-2), 3.62–3.44 (m, 1H, H-3), 3.02 (d, $J_{3,NH}=2.8$ Hz, 1H, NH), 2.30–2.23 (m, 1H, H-2′), 2.15–2.06 (m, 1H, H_A-3′), 2.03–1.85 (m, 3H, H-4, H_A-6′), 1.78–1.71 (m, 3H, H-5, H_A-4′), 1.56–1.25 (m, 6H, H-6, H-7, H-3′, H_A-5′), 1.38 (s, 9H, 3xCH_3), 1.30 (s, 3H, H-9′), 1.18 (s, 3H, H-10′), 1.01–0.92 (m, 5H, H_B-4′, H_B-6′, H-8), 0.91 (d, $J_{5',7'}=7.3$ Hz); ^{13}C NMR (50 MHz; $CDCl_3$): δ 155.4 (C=O Boc), 152.4 (i-Ar), 128.3 (Ar), 125.7 (Ar), 96.6 ($C(CH_3)_3$), 79.7 (C-1′), 72.0 (C-2), 52.6 (C-3), 50.3 (C-2′), 41.2 (C-6′), 39.8 (C-8′), 34.9 (C-4′), 33.4 (C-4), 32.1 (C-5′), 31.9 (C-5), 30.7 (C-9′), 28.9 (3xCH_3 Boc), 26.7 (C-3′), 26.3 (C-6), 23.2 (C-7′), 22.8 (C-10′), 22.3 (C-7), 14.6 (C-8).

4.3.12. *O*-[*anti*-(3ξ)-*t*-Butoxycarbonylamino-(2ξ)-hydroxyoctanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (15b). The title compound was obtained as a colourless oil, in 92% yield: (R_f=0.50 hexane/AcOEt 7:3); $[\alpha]_D{}^{20}=-10.0$ (c=0.1; $CHCl_3$); ^1H NMR (200 MHz; $CDCl_3$): δ 7.35–7.22 (m, 5H, Ar), 4.92 (dt, $J_{1',6'A}=J_{1',2'}=10.7$, $J_{1',6'B}=4.3$, 1H, H-1′), 4.60 (d, $J_{2,3}=9.5$ Hz, 1H, H-2), 3.75–3.50 (m, 1H, H-3), 3.21 (d, $J_{3,NH}=2.8$ Hz, 1H, NH), 2.30–2.25 (m, 1H, H-2′), 2.18–2.08 (m, 1H, H_A-3′), 2.03–1.84 (m, 3H, H-4, H_A-6′), 1.79–1.73 (m, 3H, H-5, H_A-4′), 1.54–1.23 (m, 6H, H-6, H-7, H-3′, H_A-5′), 1.45 (s, 9H, 3xCH_3), 1.30 (s, 3H, H-9′), 1.25 (s, 3H, H-10′), 1.11–0.98 (m, 5H, H_B-4′, H_B-6′, H-8), 0.90 (d, $J_{5',7'}=7.2$ Hz, 3H, H-7′), ^{13}C NMR (50 MHz; $CDCl_3$): δ 172.7 (C-1), 155.9 (C=O Boc), 151.7 (i-Ar), 128.8 (Ar), 125.7 (Ar), 79.7 ($C(CH_3)_3$), 76.2 (C-1′), 73.3 (C-2), 53.3 (C-3), 50.8 (C-2′), 42.1 (C-6′), 41.1 (C-8′), 34.9 (C-4′), 32.0 (C-4), 31.8 (C-5′), 29.9 (C-5), 29.6 (C-9′), 28.9 (3xCH_3 Boc), 26.8 (C-3′), 25.8 (C-6), 24.2 (C-7′), 23.0 (C-10′), 22.3 (C-7), 14.5 (C-8).

4.3.13. *O*-[syn-(3ξ)-*t*-Butoxycarbonylamino-4,4-diethoxy-(2ξ)-hydroxybutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (16a). The compound 16a was obtained as a

colourless oil in 92% yield, (R_f=0.50 hexane/AcOEt 7:3). HRMS-LSIMS(+): Calcd for $C_{29}H_{47}O_7NNa$ $(M+Na)^+$: 544.3250, found 544.3234; IR (film): 3450, 3386, 2973, 2927, 1723, 1501, 1367, 1247, 1171, 1124, 1063, 764, 701 cm^{-1}; $[\alpha]_D{}^{20}$=−4.4 (c=1.61; $CHCl_3$); ^1H NMR (200 MHz; $CDCl_3$): δ 7.40–7.10 (m, 5H, Ar), 5.05–4.75 (m, 1H, H-1′), 4.41 (d, $J_{3,4}$=6.5 Hz, 1H, H-4), 3.80–3.50 (m, 4H, H-5, H-5″, H-3), 3.11–3.05 (m, 1H, H-2), 2.14–2.02 (m, 1H, H-2′), 1.98–1.84 (m, 2H, H_A-3′, H_A-6′), 1.75–1.70 (m, 1H, H_A-4′), 1.52–1.41 (m, 1H, H_A-5′), 1.40 (s, 9H, 3xCH_3), 1.31 (s, 3H, H-9′), 1.28 (t, $J_{5,6}$=7.1 Hz, 3H, H-6), 1.22–1.15 (m, 1H, H_B-3′), 1.10–0.91 (m, 2H, H_B-4′, H_B-6′), 1.17 (t, $J_{5'',6''}$=7.1 Hz, 3H, H-6″), 1.16 (s, 3H, H-10′), 0.90 (d, $J_{5',7'}$=6.5 Hz, 3H, H-7′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 172.7 (C-1), 155.4 (C=O Boc), 151.9 (i-Ar), 128.5 (Ar), 126.0 (Ar), 125.7 (Ar), 101.9 (C-4), 79.7 ($C(CH_3)_3$), 76.7 (C-1′), 70.0 (C-2), 64.2 (C-5), 61.6 (C-5″), 53.5 (C-3), 50.6 (C-2′), 41.4 (C-6′), 40.1 (C-8′), 34.9 (C-4′), 31.9 (C-5′), 29.4 (C-9′), 28.9 (3xCH_3), 27.0 (C-8′), 24.4 (C-3′), 22.3 (C-7′, C-10′), 15.8 (C-6), 15.6 (C-6″).

4.3.14. *O*-[*anti*-(3ξ)-*t*-Butoxycarbonylamino-4,4-diethoxy-(2ξ)-hydroxybutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenyl-menthol (16b). The title compound was obtained as a colourless oil in 88% yield, (R_f=0.6 hexane/AcOEt 6:4). ^1H NMR (200 MHz; $CDCl_3$): δ 7.50–7.00 (m, 5H, Ar), 5.00–4.80 (m, 1H, H-1′), 4.41 (d, $J_{3,4}$=5.5 Hz, 1H, H-4), 3.90–3.75 (m, 1H, 1, H-3), 3.70–3.36 (m, 4H, 2H-5, H-5″), 3.20–3.02 (m, 1H, H-2), 2.13–2.01 (m, 1H, H-2′), 1.96–1.80 (m, 2H, H_A-3′, H_A-6′), 1.77–1.71 (m, 1H, H_A-4′), 1.54–1.42 (m, 1H, H_A-5′), 1.45 (s, 9H, 3xCH_3), 1.30 (s, 3H, H-9′), 1.29 (t, $J_{5,6}$=7.1 Hz, 3H, H-6), 1.23–1.15 (m, 1H, H_B-3′), 1.11–0.90 (m, 2H, H_B-4′, H_B-6′), 1.19 (t, $J_{5'',6''}$=7.1 Hz, 3H, H-6″), 1.17 (s, 3H, H-10′), 0.89 (d, $J_{5',7'}$=6.5 Hz, 3H, H-7′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 172.1 (C-1), 155.5 (C=O Boc), 151.9 (i-Ar), 128.5 (Ar), 125.7 (Ar), 125.5 (Ar), 101.5 (C-4), 79.9 ($C(CH_3)_3$), 76.0 (C-1′), 71.8 (C-2), 64.6 (C-5), 62.0 (C-5″), 53.8 (C-3), 50.7 (C-2′), 41.8 (C-6′), 40.9 (C-9′), 35.0 (C-4′), 31.8 (C-5′), 29.7 (C-9′), 28.9 (3xCH_3), 26.9 (C-8′), 24.0 (C-3′), 22.4 (C-7′, C-10′), 15.8 (C-6), 15.6 (C-6″).

4.3.15. *O*-[*anti*-(3ξ)-*t*-Butoxycarbonylamino-(2ξ)-hydroxy-3-phenylpropanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenyl-menthol (17b). The title compound was obtained as a colourless oil in 88% yield (R_f=0.5 hexane/AcOEt 8:2). HRMS-ESI: Calcd for $C_{30}H_{41}O_5NNa$ $(M+Na)^+$ 518.2882, found 518.2899; IR (KBr): 3445 2967, 1722, 1496, 1456, 1367, 1256, 1169, 700; ^1H NMR (400 MHz; $CDCl_3$): δ 7.35–7.20 (m, 7H, Ar), 7.15–7.04 (m, 3H, Ar), 5.50 (d, $J_{2,3}$=9.1 Hz, 1H, H-2), 5.00 (d, $J_{2,3}$=9.1 Hz, 1H, H-3), 4.93 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.4 Hz, 1H, H-1′), 3.91 (bs, 1H, NH), 2.19–2.10 (m, 1H, H-2′), 1.94–1.85 (m, 1H, H_A-3′), 1.80–1.73 (m, 1H, H_A-6′), 1.71–1.66 (m, 1H, H_A-4′), 1.52 (s, 9H, 3xCH_3), 1.50–1.40 (m, 1H, H_A-5′), 1.31 (s, 3H, H-9′), 1.28–1.21 (m, 1H, H_B-3′), 1.19 (s, 3H, H-10′), 1.01–0.89 (m, 2H, H_B-4′, H_B-6′), 0.86 (d, $J_{5',7'}$=6.6 Hz, 3H, H-7′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 170.5 (C-1), 154.7 (C=O Boc), 152.2 (i-Ar), 139.4 (i-Ar), 128.2 (Ar), 127.9 (Ar), 127.3 (Ar), 126.6 (Ar), 125.3 (Ar), 79.3 ($C(CH_3)_3$ Boc), 76.1 (C-1′), 74.3 (C-2), 55.7 (C-3), 49.9 (C-2′), 41.1 (C-6′), 39.4 (C-8′), 34.2 (C-4′), 31.2 (C-5′), 28.3 (C-9′), 27.3 (3xCH_3 Boc), 26.1 (C-3′), 22.5 (C-7′), 21.6 (C-10′).

4.4. General procedure of isopropylidene formation

A solution of *N*-Boc-aminoalcohols (0.19 mmol), dimethoxy-propane (0.21 mmol) and catalytic amounts of TsOH in toluene (2 mL) was heated at 50 °C. Progress of the reaction was monitored by TLC. After 5 h the mixture was cooled, solvents were evaporated and the residue was purified on silica gel using hexane/AcOEt (9:1–7:3).

4.4.1. *O*-[*anti*-(3ξ)-*t*-Butoxycarbonylamino-(2ξ)-hydroxy-2,3-isopropylideneoctanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenyl-menthol (18a). The compound was obtained as a colourless oil in 86%. HRMS-ESI: Calcd for $C_{32}H_{51}O_5NNa$ $(M+Na)^+$: 552.3659, found: 552.3666; IR (film): 2955, 2923, 2860, 1747, 1699, 1456, 1381, 1213, 1104, 1061, 769, 701 cm^{-1}; R_f=0.5 (hexane/AcOEt 8:2); $[\alpha]_D{}^{20}$=8.6 (c=1.70; $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 7.30–7.24 (m, 4H, Ar), 7.15–7.09 (m, 1H, Ar), 4.90 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.7 Hz, $J_{1',6'B}$=4.4 Hz, 1H, H-1′), 3.77–3.74 (m, 1H, H-3), 3.29 (d, $J_{2,3}$=2.7 Hz, 1H, H-2), 2.05–1.98 (m, 1H, H-2′), 2.13–2.04 (m, 1H, H_A-3′), 2.01–1.80 (m, 3H, H-4, H_A-6′), 1.78–1.72 (m, 3H, H-5, H_A-4′), 1.55–1.25 (m, 6H, H-6, H-7, H-3′, H_A-5′), 1.47 (s, 6H, 2xCH_3), 1.42 (s, 9H, 3xCH_3), 1.29 (s, 3H, H-9′), 1.18 (s, 3H, H-10′), 1.02–0.91 (m, 2H, H_B-4′, H_B-6′), 0.91 (t, $J_{7,8}$=7.5 Hz, 3H, H-8), 0.87 (d, $J_{5',7'}$=7.3 Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 170.7 (C-1), 151.7 (C=O Boc), 128.0 (Ar), 125.3 (Ar), 124.9 (Ar), 95.6 ($C(CH_3)_2$), 80.0 ($C(CH_3)_2$), 74.6 (C-1′), 60.6 (C-2), 50.5 (C-2′), 41.6 (C-6′), 39.4 (C-8′), 34.4 (C-4′), 31.4 (C-5), 31.2 (C-5′), 28.8 (C-9′), 28.3 (5xCH_3), 26.3 (C-3′), 24.8 (C-6), 23.5 (C-7′), 22.6 (C-7), 21.6 (C-10′), 14.0 (C-8).

4.4.2. *O*-[*syn*-(3ξ)-*t*-Butoxycarbonylamino-(2ξ)-hydroxy-2,3-isopropylideneoctanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenyl-menthol (18b). The title compound was obtained in 84% yield. R_f=0.45 (hexane/AcOEt; colourless oil, $[\alpha]_D{}^{20}$=−10.8 (c=0.77; $CHCl_3$); ^1H NMR (500 MHz; $CDCl_3$): δ 7.31–7.24 (m, 4H, Ar), 7.15–7.08 (m, 1H, Ar), 4.97–4.94 (m, 1H, H-1′), 3.54–3.50 (m, 1H, H-3), 3.23–3.20 (m, 1H, H-2), 2.05–1.99 (m, 1H, H-2′), 2.12–2.04 (m, 1H, H_A-3′), 2.04–1.83 (m, 3H, H-4, H_A-6′), 1.79–1.71 (m, 3H, H-5, H_A-4′), 1.58–1.26 (m, 6H, H-6, H-7, H-3′, H_A-5′), 1.48 (s, 6H, 2xCH_3), 1.43 (s, 9H, 3xCH_3), 1.31 (s, 3H, H-9′), 1.19 (s, 3H, H-10′), 1.02–0.90 (m, 5H, H_B-4′, H_B-6′, H-8), 0.89 (d, $J_{5',7'}$=7.6 Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 167.0 (C-1), 152.0 (C=O Boc), 151.6 (*i*-Ar), 127.9 (Ar), 125.2 (Ar), 124.8 (Ar), 93.8 ($C(CH_3)_2$), 79.6 ($C(CH_3)_2$), 74.9 (C-1′), 50.1 (C-2′), 41.4 (C-6′), 40.2 (C-8′), 34.4 (C-4′), 31.9 (C-5), 31.0 (C-5′), 30.3 (C-9′), 28.4 (5xCH_3), 26.4 (C-3′), 24.9 (C-6), 23.5 (C-7′), 22.4 (C-7), 21.7 (C-10′), 13.9 (C-8).

4.4.3. *O*-[*anti*-(3ξ)-Amino-4,4-diethoxy-(2ξ)-hydroxy-2,3-isopropylidenebutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenyl-menthol (19a). The title compound was obtained as a colourless oil in 85% yield, (R_f=0.5 hexane/AcOEt 8:2). HRMS-LSIMS(+): Calcd for $C_{24}H_{43}O_5NNa$ $(M+Na)^+$: 484.6302, found 484.6308; IR (film): 3455, 2957, 2926, 1705, 1496, 1456, 1391, 1366, 1257, 1173, 1150, 1119, 765, 701 cm^{-1}; $[\alpha]_D{}^{20}$=−4.4 (c=1.61; $CHCl_3$); ^1H NMR (500 MHz; C_6D_6): δ 7.20–6.90 (m, 5H, Ar), 5.00 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.8 Hz, $J_{1',6'B}$=4.4 Hz, 1H, H-1′), 4.74 (d,

$J_{3,4}$=1.5 Hz, 1H, H-4), 3.85 (dd, $J_{3,4}$=1.5 Hz, $J_{3,2}$=8.6 Hz, 1H, H-3), 3.75 (ddd, $J_{5A,5B}$=9.6 Hz, $J_{5A,6}$=7.1 Hz, $J_{5B,6}$= 7.0 Hz, 2H, H-5), 3.42 (dd, $J_{5''A,5''B}$=9.6 Hz, $J_{5A'',6''}$= 7.1 Hz, $J_{5B'',6''}$=7.0 Hz, 2H, H-5″), 3.37 (d, $J_{3,2}$=8.6 Hz, 1H, H-2), 2.00–1.90 (m, 3H, H-2′, H_A-3′, H_A-6′), 1.75–1.68 (m, 1H, H_A-4′), 1.55–1.45 (m, 1H, H_A-5′), 1.24 (s, 6H, 3xCH_3), 1.23–1.17 (m, 1H, H_B-3′), 1.15–0.92 (m, 2H, H_B-4′, H_B-6′), 1.12 (s, 3H, H-9′), 1.00–0.92 (m, 6H, H-6, H-6″), 1.12 (s, 3H, H-10′), 0.69 (d, $J_{5',7'}$=6.5 Hz, 3H, H-7′); ^{13}C NMR (50 MHz; $CDCl_3$): δ 168.0 (C-1), 152.9 (i-Ar), 128.7 (Ar), 125.8 (Ar), 125.6 (Ar), 99.9 (C-4), 97.8 ($C(CH_3)_2$), 75.7 (C-1′), 74.9 (C-2), 66.2 (C-5), 62.9 (C-5″), 51.2 (C-3), 42.3 (C-2′), 39.8 (C-6′), 39.1 (C-8′), 35.0 (C-4′), 31.7 (C-5′), 31.2 (C-9′), 29.2 (2xCH_3), 27.0 (C-8′), 26.5 (C-3′), 23.9 (C-7′), 22.3 (C-10′), 15.8 (C-6), 15.6 (C-6″).

4.4.4. *O*-[3-*O*-[*syn*-(3ξ)-Amino-4,4-diethoxy-(2ξ)-hydroxy-2,3-isopropylidenebutanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (19b). The title compound was obtained as a colourless oil in 84% yield (R_f=0.50 hexane/AcOEt 8:2): ^{1}H NMR (500 MHz; C_6D_6): δ 7.20–6.90 (m, 5H, Ar), 5.22 (d, $J_{3,4}$=1.8 Hz, 1H, H-4), 4.92 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.4 Hz, $J_{1',6'B}$=4.4 Hz, 1H, H-1′), 3.87 (dd, $J_{3,4}$=1.8 Hz, $J_{3,2}$=7.8 Hz, 1H, H-3), 3.70–3.65 (m, 2H, H-5), 3.49–3.41 (m, 2H, H-5″), 3.44 (d, $J_{3,2}$=7.8 Hz, 1H, H-2), 2.01–1.92 (m, 3H, H-2′, H_A-3′, H_A-6′), 1.78–1.69 (m, 1H, H_A-4′), 1.56–1.47 (m, 1H, H_A-5′), 1.25 (s, 6H, 3xCH_3), 1.23–1.16 (m, 1H, H_B-3′), 1.15–0.90 (m, 2H, H_B-4′, H_B-6′), 1.13 (s, 3H, H-9′), 1.00–0.91 (m, 6H, H-6, H-6″), 1.15 (s, 3H, H-10′), 0.70 (d, $J_{5',7'}$=6.5 Hz, 3H, H-7′).

4.4.5. *O*-[*syn*-(3ξ)-*t*-Butoxycarbonylamino-(2ξ)-hydroxy-2,3-isopropylidene-3-phenyl-propanoyl]-(1′*R*,2′*S*,5′*R*)-8′-phenylmenthol (20b). The title compound was obtained as a colourless oil in 90% yield, (R_f=0.6 hexane/AcOEt 8:2). HRMS-ESI: Calcd for $C_{33}H_{45}O_5N$ $(M+H)^+$ 558.3190, found 558.3182; IR (KBr): 2959, 2927, 1730, 1703, 1456, 1378, 1366, 1255, 1177, 1099, 764, 700 cm^{-1}; $[\alpha]_D^{20}$=−1.75 (c=1.17; $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.20–6.80 (m, 10H, Ar), 5.48 (bs, 1H, H-2), 5.01 (dt, $J_{1',6'A}$=$J_{1',2'}$=10.6 Hz, $J_{1',6'B}$=4.4 Hz, 1H, H-1′), 3.89 (bs, 1H, H-3), 2.17–2.10 (m, 1H, H-2′), 1.95–1.88 (m, 1H, H_A-3′), 1.81–1.75 (m, 1H, H_A-6′), 1.72–1.69 (m, 1H, H_A-4′), 1.48–1.40 (m, 1H, H_A-5′), 1.21 (s, 3H, H-9′), 1.17 (bs, 9H, H-10′, 2xCH_3), 1.22–1.19 (m, 1H, H_B-3′), 1.06 (s, 9H, 3xCH_3), 1.01–0.90 (m, 2H, H_B-4′, H_B-6′), 0.67 (d, $J_{5',7'}$=6.3 Hz, 3H, H-7′); ^{13}C NMR (125 MHz; $CDCl_3$): δ 169.9 (C-1), 152.1 (C═O Boc), 151.4 (i-Ar), 128.7 (Ar), 128.4 (Ar), 127.9 (Ar), 125.8 (Ar), 125.5 (Ar), 96.6 ($C(CH_3)_2$), 81.3 (C-2), 80.6 ($C(CH_3)_3$ Boc), 76.2 (C-1′), 62.9 (C-3), 50.6 (C-2′), 41.9 (C-6′), 40.2 (C-8′), 34.9 (C-4′), 31.9 (C-5′), 28.3 (C-9′), 27.1 (C-3′), 25.3 (C-7′), 22.3 (C-10′).

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Chemistry of odorants: stereoselective synthesis of octahydronaphthalene-based perfumery *Georgywood*, (+,−)-1-[(1*R* *,2*S* *)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one

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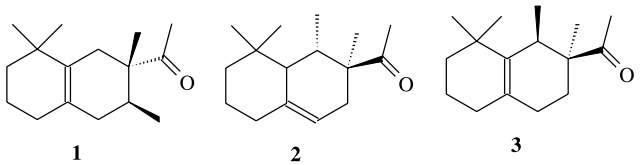
Abstract—A straightforward synthesis of octahydronaphthalene-based fragrance, such as *Georgywood*, is described. The Lewis acid tin (IV) chloride catalyzed efficiently an original one-pot sequential cycloaddition–clyclization process by reaction of myrcene with 3-bromo-but-3-en-2-one, leading directly to the octahydronaphthalene skeleton in very good yields (85%). Then, dehydrohalogenation with DBU gave the key 2,4-dienone intermediate in excellent yield (85%). Regioselective Michael addition gave rise to the formation of the addition product as a *trans*/*cis* diastereoisomeric mixture, by reaction either with $CH_3Cu{\cdot}BF_3$ (6:1 ratio, 70%) or $(CH_3)_2CuLi$/TMSCl reagents (3:1 ratio, 80%). The generation of thermodynamically more stable enolate by treatment of the diastereoisomeric mixture with sodium hydride in tetrahydrofuran in the presence of an excess of methyl iodide, allowed stereoselective introduction of the methyl group at C2, leading to the formation of *Georgywood* in good yield (60%), as the only diastereoisomer, with a *trans* stereochemistry of the two methyl groups as demonstrated by NMR experiments.

1. Introduction

The octahydronaphthalene skeleton constitutes a structural requirement of industrially significant fragrances, such as *Iso E Super*® **1**, its powerful minor constituent **2**, and *Georgywood* **3** (Fig. 1).[1] All the compounds fulfil the above structural requirements, possessing a rich, warm-woody odor with a shade of amber.[2] The industrial synthesis of **1** starts with the aluminium trichloride catalyzed Diels–Alder reaction of myrcene with (3*E*)-3-methylpent-3-en-2-one, followed by a cyclization reaction of the substituted cyclohexene intermediate in presence of sulfuric acid, which leads to **1**. Surprisingly, it was found that it is not the main component **1** but ca. 5% constituent **2** that determines the woody-amber odor of commercially *Iso E Super*® **1**.[3] The formation of **2** as a by-product during the synthesis of **1** was rationalized by an acid-catalyzed rearrangement of olefinic intermediates. As a consequence, numerous structural analogues of **2** were synthesized, of which *Georgywood* **3** was found to be one of best, showing the same odor threshold and possessing a very attractive warm-woody, sweet-powdery smell.[4]



1 2 3

Figure 1. Structures of compounds **1**, **2** and **3**.

The strategy for the synthesis of *Georgywood* **3** includes the well-known and previously described two step sequence: first, the Lewis acid-activated Diels–Alder reaction of homomyrcene[5] with methyl isopropenyl ketone, then the subsequent acid-catalyzed cyclization of the cyclohexene intermediate to **3**.[5] In this publication, we report a new synthesis of octahydronaphthalene-type odorants, such as **3**, by a general strategy which should make the bicyclic intermediates synthetically more accessible. It was our particular aim to find a simplified synthetic strategy, and to be guided by readily available starting materials in conjunction with straightforward chemistry.

Keywords: Odorants; *Georgywood*; Diels–Alder reactions; Octahydronaphthalene skeleton; Lewis acid mediated conjugate addition.
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2. Results and discussion

2.1. Synthesis of octahydronaphthalene skeleton

Our strategy commenced with the construction of the octahydronaphthalene skeleton. We had in mind to find a protocol, which should easily access the bicyclic framework through a one-pot process. This goal was addressed performing an original domino sequence by a tin (IV) chloride-catalyzed Diels–Alder reaction of myrcene **4** with 3-bromo-but-3-en-2-one **5**. The reaction was carried out in CH_2Cl_2 at −78 °C, and we observed the direct formation of the desired ethanone,1-(2-bromo-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl) **6** as the only regioisomer in 85% yield (Scheme 1) (Table 1, entry 5). The outcome of the reaction can be explained first with a $SnCl_4$ oriented Diels–Alder reaction,[6,7] immediately followed by an intramolecular cyclization of the unsaturated cyclohexene intermediate, such as **7**, to give **6**.[8,9] To the best of our knowledge, there are no examples of the direct synthesis of such molecules by a $SnCl_4$-guided one-pot sequential cycloaddition–cyclization process.[1]

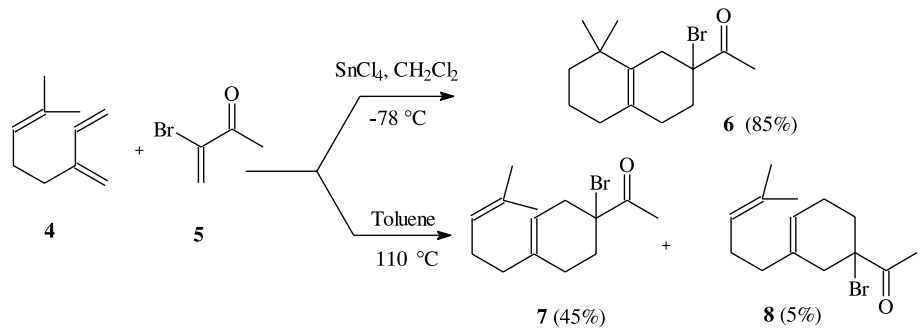
It is worth noting that the thermal uncatalyzed cycloaddition of myrcene with methyl vinyl ketone is described to give rise to a mixture of two regioisomeric cyclohexene derivatives.[8b,10]

However, when the reaction was carried in toluene at 25 °C and with $SnCl_4$ as catalyst, a mixture of the two regioisomeric cycloaddition adducts **7** and **8** was obtained, with a 80:20 ratio and a 50% yield (Table 1, entry 4). The use of a different Lewis acid as catalyst, such as $BF_3{\cdot}Et_2O$ in CH_2Cl_2 at 25 °C, gave a mixture of the two regioisomers **7** and **8**, with a 80:20 ratio and a poor yield (25%) (Table 1, entry 3).[11] The results show that tin (IV) chloride plays a pivotal role. Probably, the donor–acceptor interaction between the dienophile and the catalyst lowers the LUMO energy of the dienophile, favoring the stabilization of a sterically less crowded *endo* transition state.[12] As a consequence, the Lewis acid catalyzed cycloaddition proceeded faster and more regioselectively than the thermal counterpart, giving first the monocyclic adduct,[6,12] such as **7**, then promoting the intramolecular cyclization reaction to the octahydronaphthalene derivative **6**. The capability of tin (IV) chloride to act as promoter of intramolecular cyclization reactions has been described many times. For instance, Saito,[9a,b] Kawanobe and co-workers[9c] studied the $SnCl_4$-mediated cyclization of both homofarnesoic acid and monocyclo homofarnesoic acid to racemic sclareolide. Furthermore, the formation of any regioisomeric octahydronaphthalene derivative, such as **9** (Fig. 2), was never detected according to the above experimental procedure.

Performing the uncatalyzed cycloaddition process, toluene was needed as solvent and higher temperatures were required: at 60 °C, the regioisomeric cyclohexene derivative **7** was obtained with a 30% yield, while at 110 °C the two regioisomers **7** and **8** were formed with a 50% yield and a 90:10 ratio (Scheme 1) (Table 1, entries 1 and 2, respectively). Moreover, the formation of octahydronaphthalene derivatives, such as **6**, was never detected under these experimental conditions. Finally, **7** was cyclized with concentrated sulfuric acid into the corresponding octahydronaphthalene skeleton **6**, in agreement with the regiochemistry of the cycloaddition reaction.[8b,10]

2.2. Dehydrohalogenation

The next step was the dehydrohalogenation of **6** to get 1-(8,8-dimethyl-3,4,5,6,7,8-hexahydronaphthalen-2-yl)ethan-1-one **10**. The elimination reaction was efficiently carried out by treatment **6** with DBU in CH_2Cl_2 as solvent at 0 °C, 24 h;[8b,10a] the 2,4-dienone **10** was obtained with a 85% yield. The same reaction on **7** led to 1-[4-(4-methyl-3-

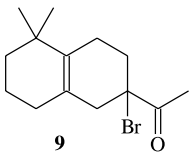


Scheme 1. Synthesis of **6**, **7** and **8**.

Table 1. The Diels–Alder reaction of myrcene **4** with 3-bromo-pent-2-en-3-one **5**

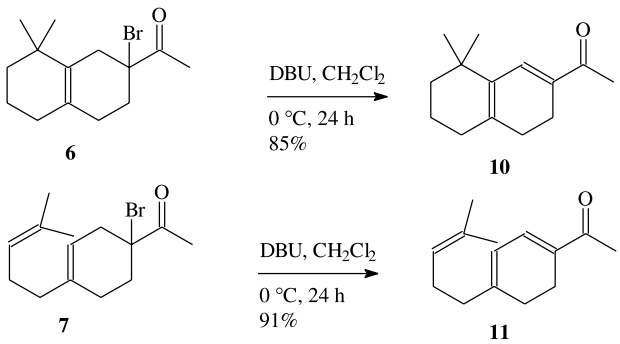
Entry	Catalyst (equiv.)	Solvent	Reaction time (h)	Temperature (°C)	Products	Yield (%)	Ratio[a]
1	—	Toluene	24	60	**7**	30	100:0
2	—	Toluene	48	110	**7**+**8**	50	90:10
3	$BF_3{\cdot}OEt_2$ (0.1)	CH_2Cl_2	1	25	**7**+**8**	25	80:20
4	$SnCl_4$ (0.1)	Toluene	1	0	**7**+**8**	50	80:20
5	$SnCl_4$ (0.3)	CH_2Cl_2	4	−78	**6**	85	100:0

[a] Determined by GC-MS analysis.



9

Figure 2. Structure of compound **9**.



6 10

7 11

Scheme 2. Synthesis of **10** and **11**.

pentenyl)-1,3-cyclohexadienyl]ethan-1-one **11** with a 91% yield.(Scheme 2).

Other reagents, such as Al_2O_3 or pyridine, gave poor yields of **10**.

2.3. Conjugate addition

Activated 2,4-dienones, such as **10** and **11**, can provide several isomeric products in copper-mediated Michael addition reactions. Besides direct nucleophilic attack at the carbonyl group, **10** and **11** can undergo 1,4 or 1,6-addition, giving rise to a mixture of three regioisomeric substituted cycloalkenes which contain new stereogenic centers.[13] As a consequence, the major challenge was control of the regio- and stereoselectivity of the Michael addition.[13c]

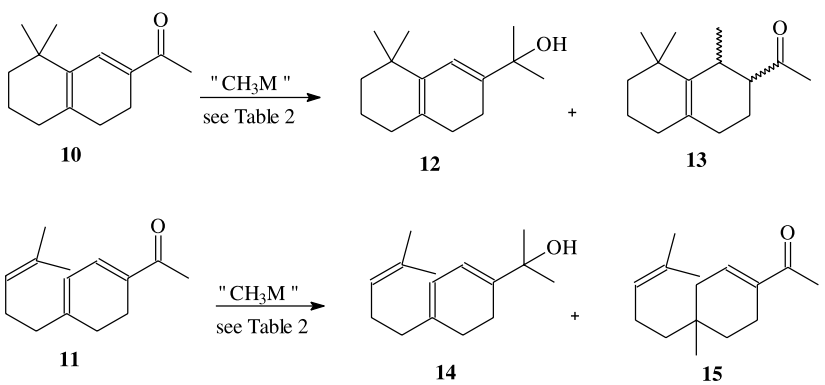
Thus, many different combinations of copper(I) salts, organometallic compounds and solvents have been employed to study the reactivity, the efficiency and the selectivity of the 2,4-dienones as Michael acceptor for the introduction of a methyl group at C1 of **10** and at C2 of **11**.(Table 2).

It was found that under the conditions usually employed for metallo-assisted 1,4-Michael additions,[16] i.e. by treatment with the Grignard reagent, with or without copper (I) salts as catalyst,[13,16] (Table 1, entries 1, 2, 3 and 6), dimethyl-lithiumcuprate (entries 4 and 5), methyl lithium and HMPT or DMPU as co-solvents (entries 7 and 8),[17] methyl lithium and cumene (entries 9 and 10),[18] both dienones **10** and **11** were almost unreactive and the 1,4-Michael addition reactions proceeded unsuccessfully. We observed the

Table 2. Michael addition to 2,4-dienones **10** and **11**

Entry	Substrate	Reagent (equiv.)	Solvent	Temperature (°C)	Product (yield, %)[a]
1	**10**	CH_3MgCl (1)[14,15]	THF	−78	**12** (40)
2	**11**	CH_3MgCl (1)[15,16]	Et_2O	−78	**14** (tr), **15** (tr)
3	**10**	$(CH_3)_2CuMgCl$	THF	−78	**12** (15), **13** (tr)
4	**11**	$(CH_3)_2CuLi$ (1.5)	Et_2O	−78	**15** (tr)
5	**10**	$(CH_3)_2CuLi$ (1)[15]	THF	−78	—
6	**10**	CH_3MgCl (3), CuI (0.05)	Et_2O	−78/0	**12** (tr), **13** (tr)
7	**10**	CH_3Li (1) HMPT[17]	*n*-Hexane	−78	**12** (tr)
8	**10**	CH_3Li (1.5) DMPU	*n*-Hexane	−78	—
9	**10**	CH_3Li·cumene (1)[18]	THF	−78	**12** (tr)
10	**10**	CH_3Li·cumene. (1) HMPT[18]	THF	−78	**12** (tr), **13** (tr)
11	**11**	$CuCH_3{\cdot}BF_3$ (6)	Et_2O	−78	**15** (65)
12	**10**	$CuCH_3{\cdot}BF_3$ (1)	Et_2O	−78	**13** (15)
13	**10**	$CuCH_3{\cdot}BF_3$ (3)	Et_2O	−78	**12** (12), **13** (40)
14	**10**	$CuCH_3{\cdot}BF_3$ (6)	Et_2O	−78	**12** (24), **13** (70)
15	**10**	$(CH_3)_2CuLi$. TMSCl (3)[19]	Et_2O	−78	**12** (15), **13** (80)

[a] Determined by GC-MS analysis.



10 12 13

11 14 15

Scheme 3. Synthesis of **13** and **15**.

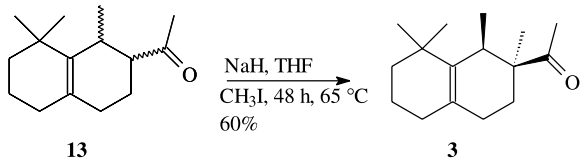
formation of the 1,2-adduct **12** in poor yields (entries 1 and 2) (Scheme 3).

In recent past years, Yamamoto described the Lewis acid-mediated reactions of organocopper reagents with various kinds of α,β-unsaturated carbonyl compounds.[20] Particularly, RCu·BF_3 has found favor as a valued Michael donor in couplings with α,β-γ,δ-unsaturated ketones, esters, and even acids.[21] As reported, methyl sorbate undergoes a 1,4-addition via BuCu·BF_3, while undergoing a 1,6-α,δ-addition via Bu_2CuLi.[22] Prompted by these findings, we exploited the reactivity of the Yamamoto's reagent ($CH_3Cu·BF_3$) with the dienones **10** and **11** (Scheme 3). Actually, the 2,4-dienone **11** reacted with the Yamamoto's reagent to provide with complete 1,6-regioselectivity the enone **15** in 65% yield (entry 11). On the other hand, the reaction of the 2,4-dienone **10** with $CH_3Cu·BF_3$ gave preferentially the desired 1,4-adduct **13**, together with small quantities of 1,2-adduct **12** as a side-product (entries 12, 13 and 14).[15b] Surprisingly, the enone **10** was unreactive as a 1,6-Michael acceptor, probably due to the sterically more crowded γ,δ-double bond. The best yields were obtained with a 1:6 substrate/reagent ratio (entry 14). Furthermore, by treatment with dimethyl lithium cuprate activated with TMSCl as a soft Lewis acid, the dienone **10** provided the desired enone **13** in good yield (80%), while the formation of the side-product **12** decreased.[19,23] The enone **13** was obtained as an inseparable diastereoisomeric mixture, the diastereoselectivity varying from 6:1 to 3:1 *trans*/*cis* ratio with Yamamoto's reagent and with $(CH_3)_2CuLi$/TMSCl reagent, respectively.[24] The stereochemistry of the two diastereoisomers was established by ^1H NMR analysis: *trans* isomer: CH_3 at C1, 0.87 δ, d (J=6.6 Hz); CH_3CO, 2.17 δ, s; H_a–C1/H_b–C2, J=11.0 Hz, in agreement with a *trans*–*anti* relationship; *cis* isomer: CH_3 at C1, 1.17 δ, d (J=6.6 Hz); CH_3CO, 2.13 δ, s, in agreement with their *cis* relationship.[20b]

It is worth noting that octahydronaphthalene derivatives, such as **13**, are valuable compounds in the chemistry of fragrances.[5b] Furthermore, the results show the flexibility of our strategy, allowing to prepare a library of differently C1 alkyl-substituted octahydronaphthalenes by reaction of the dienone **10** with suitable organocopper reagents, such as RCu·BF_3 or R_2CuLi/TMSCl.

2.4. Synthesis of (+,−)-1-[(1*R**,2*S**)-1,2,3,4,5,6,7,8-octahydro-1,2,8,8-tetramethylnaphthalen-2-yl)ethan-1-one, *Georgywood*, 3

All the experiments for a one-pot sequential alkylation of the ketone enolate generated by organo copper conjugate addition failed, both utilizing CH_3I or CH_3OTf as electrophiles and HMPA as co-solvent.[25] To overcome this limitation, the introduction of a methyl group at C2 was successfully addressed by performing the alkylation reaction directly on the diastereoisomeric mixture **13**. The conversion was performed through the generation of thermodynamically more stable enolate with sodium hydride in tetrahydrofuran in the presence of an excess of methyl iodide,[26] leading to the formation of **3** in 60% yield, as the only diastereoisomer (Scheme 4). Interestingly, the alkylation reaction was completely diastereoselective,



13 **3**

(*trans*/*cis* diastereoisomeric mixture)

Scheme 4. Synthesis of *Georgywood* **3**.

giving rise to the formation of only the compound **3**. By GC co-injection and NMR spectra, the synthetic material **3** proved to be totally identical with an authentic sample of the well-known fragrance *Georgywood*.[5b,c]

3. Conclusion

We have demonstrated that the octahydronaphthalene skeleton can be directly and readily achieved in high yields and regioselectivity by an original tin (IV) chloride-catalyzed domino process, characterized by a sequence of an intermolecular oriented Diels–Alder reaction, immediately followed by an intramoleculr cyclization to give the bicyclo compound. This new procedure leading to the bicyclo skeleton shortened the previously reported two-step sequences. The key-intermediate, the 2,4-dienone **10**, gave an excellent performance in regio- and stereoselective double alkylation reactions, making the target compound easily available. Therefore, these new transformations can be efficiently utilized in target-oriented syntheses.

Finally, the results show the good flexibility of our strategy, which allows preparation of a library of differently alkyl-substituted octahydronaphthalenes, valuable in the chemistry of odorants. Future research in this area will concentrate on the further development of new catalytic and enantioselective transformations.

4. Experimental

4.1. General

Solvents were purified and dried by standard procedures and kept over a drying agent before use. Organometallic compounds were prepared or purchased as previously described.[27] Other reagents were purchased from commercial suppliers and were used without purification. Analytical TLC was performed using silica gel 60 F_{254} plates (Merck) and detected by treatment with a solution of H_2SO_4 2 N. Column chromatography was performed using silica gel 60 (0.063–0.200 nm) (Merck) and flash chromatography using silica gel 60 (0.040–0.063) (Merck). GC-MS analyses were performed with Hewlett–Packard GC 5890 coupled with Hewlett–Packard MS 5971A and Hewlett–Packard PC 9000. IR spectra were recorded on IR-470 infrared spectrophotometer Shimadzu. HRMS spectra were recorded with Micromass Q-TOF *micro* Mass Spectrometer (Waters). ^1H NMR and ^{13}C NMR were recorded on a VARIAN GEMINI 200 MHz spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ as solvent and as internal standard, unless stated otherwise. All chemical shifts are expressed in parts per million relative to $CDCl_3$

(δ=7.27). Spin–spin coupling constants in Hz (J) were measured directly from the spectra. The assignment of peaks in the ^{13}C NMR spectra was made by APT experiments.

4.1.1. 1-(2-Bromo-8,8-dimethyl-1,2,3,4,5,6,7,8-octahydro-2-naphthalenyl)ethan-1-one, 6. 3-Bromo-but-3-en-2-one **5**[28] (2.1 g, 14 mmol) in dry CH_2Cl_2 (40 mL) was stirred with $SnCl_4$ (1.08 g, 0.41 mmol), at −78 °C under argon for 30 min, then myrcene (1.9 g, 14 mmol) was added dropwise and the reaction mixture was stirred for 4 h and then was allowed to warm up to room temperature. The organic solution, washed with water (2×10 mL), saturated aqueous solution $NaHCO_3$ (2×10 mL) and water (10 mL) until neutrality, brine (5 mL) and dried over anhydrous Na_2SO_4, was concentrated in vacuo and purified by flash chromatography (hexane/ethyl acetate 9/1) to give **6** as viscous oil (3.39 g, yield 85%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1715, 1371, 1358, 1217, 1111. ^1H NMR (δ, $CDCl_3$): 2.80–2.57 (1H, m); 2.41 (3H, s); 2.29–2.10 (4H, m); 1.85 (2H, m); 1.68–1.54 (3H, m); 1.49–1.44 (2H, m); 1.0 (6H, s). ^{13}C NMR (δ, $CDCl_3$): 211.2 (C=O); 131.9, 126.2 (C quat); 68.5 (C–Br); 39.4; 36.1 (C quat); 33.7; 32.9; 26.8; 26.9; 24.1; 20.9; 19.9. HRMS calcd for $C_{14}H_{21}$ ^{79}BrO $[M+NH_4]^+$ 302.0776, found 302.0778.

4.1.2. 1-[1-Bromo-4-(4-methyl-3-pentenyl)-3-cyclohexenyl]ethan-1-one, 7 and 1-[1-Bromo-3-(4-methyl-3-pentenyl)-3-cyclohexenyl]ethan-1-one, 8. A stirred solution of 3-bromo-but-3-en-2-one **5** (2.1 g, 14 mmol) and myrcene (1.9 g, 14 mmol) in dry toluene (20 mL) was heated under reflux. After 48 h, the reaction mixture was cooled to room temperature and the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (25 mL) and washed with water (10 mL), brine (5 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude product was purified by flash chromatography (hexane/ethyl acetate 20/1) to give **7** (1.8 g, yield 45%) and **8** (200 mg, yield 5%), both as viscous oils.

Compound **7**. IR ν_{max} ($CHCl_3$)/cm^{-1}: 1714, 1361, 1215, 1109. ^1H NMR (δ, $CDCl_3$): 5.25 (1H, m); 5.01 (1H, m); 2.81–2.58 (2H, m); 2.35 (3H, s); 2.24–1.93 (8H, m); 1.62 (3H, s); 1.54 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 196.1 (C=O); 147.1; 131.1, 123.5 (Cquat); 122.5; 69.1 (CBr); 39.0; 36.1; 33.7; 33.1; 30.1; 27.5; 27.2; 19.0. HRMS calcd for $C_{14}H_{21}^{79}BrO$ $[M+NH_4]^+$ 302.0776, found 302.0777.

Compound **8**. IR ν_{max} ($CHCl_3$)/cm^{-1}: 1713, 1358, 1217, 1110. ^{13}C NMR (δ, $CDCl_3$): 195.5 (C=O); 143.3; 133.7, 123.9 (Cquat) 123.0; 67.2 (CBr); 39.8; 38.4; 33.6; 33.1; 29.6; 27.5; 27.3; 19.1. HRMS calcd for $C_{14}H_{21}^{79}BrO$ $[M+NH_4]^+$ 302.0776, found 302.0779.

Compound **7** (0.2 g) was dissolved in toluene (5 mL) and was added dropwise to 0.7 g of a 60% H_2S0_4 ice-cooled solution. The yellow solution was then stirred at 40 °C. After 2 h, the organic layer was washed with water (2×10 mL), saturated bicarbonate solution (3×10 mL), brine (2×5 mL), dried over Na_2SO_4 and concentrated in vacuo to give a crude product that was purified by flash chromatography (hexane/ethyl acetate 9/1) to provide **6** (140 mg, yield 70%).

4.1.3. 1-(3,4,5,6,7,8-Hexahydro-8,8-dimethyl-2-naphthalenyl)ethan-1-one, 10. To a stirred solution of **6** (1.0 g, 3.5 mmol) in dry CH_2Cl_2 (5 mL), DBU (1.06 g, 7.0 mmol) was added dropwise at 0 °C under argon. After 24 h, the organic layer was washed with a saturated aqueous solution of $CuSO_4$ (until blue color disappeared), water (10 mL), brine (5 mL), dried over Na_2SO_4 and concentrated in vacuo to give a crude product that was purified by flash chromatography (hexane/ethyl acetate 20/1) to provide **10** as viscous oil (610 mg, yield 85%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1680, 1630, 1360, 1210, 1111. ^1H NMR (δ, $CDCl_3$): 7.04 (1H, s); 2.33 (3H, s); 2.12–2.07 (4H, m); 1.70–1.58 (3H, m); 1.53–1.48 (3H, m); 1.06 (6H, s). ^{13}C NMR (δ, $CDCl_3$): 198.3 (C=O); 139.5, 134.8, 134.5 (C quat); 135.5; 38.9; 32.5 (C quat); 31.5; 29.3; 28.6; 25.1; 20.2; 19.1. HRMS calcd for $C_{14}H_{20}O$ $[M+NH_4]^+$ 222.1514, found 222.1517.

4.1.4. 1-[4-(4-Methyl-3-pentenyl)-1,3-cyclohexadienyl]ethan-1-one, 11. Compound **7** (1.0 g, 3.5 mmol) and DBU (1.06 g, 7.0 mmol), under the same reaction conditions and purification to prepare **10**, gave **11** as viscous oil (651 mg, yield 91%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1680, 1640, 1369, 1217, 1110. ^1H NMR (δ, $CDCl_3$): 6.83 (1H, d, J=6.1 Hz); 5.79 (1H, d, J=6.1 Hz); 5.02 (1H, m); 2.37 (1H, m); 2.32 (1H, m); 2.23 (3H, s); 2.15 (1H, s); 2.12 (5H, m); 1.61 (3H, s); 1.53 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 198.1 (C=O); 150.2; 135.3; 134.0; 132.2; 123.5; 118.9; 37.6; 27.5; 26.0; 25.7; 25.0; 20.4; 17.7. HRMS calcd for $C_{14}H_{20}O$ $[M+NH_4]^+$ 222.1514, found 222.1519.

4.1.5. 1-(1,2,3,4,5,6,7,8-Octahydro-1,8,8-trimethyl-naphthalen-2-yl]ethan-1-one, 13 (as inseparable *trans*/*cis* diastereoisomeric mixture). *Method a*. (Yamamoto's reagent) CuI (570 mg, 3.0 mmol) in dry Et_2O (5 mL) was treated dropwise with a 1.5 M THF solution of MeLi (2 mL, 3.0 mmol, 1) under argon at 0 °C. Then $BF_3{\cdot}Et_2O$ (0.4 mL, 3.0 mmol) was added dropwise at −78 °C and stirred. After 20 min, **10** (102 mg, 0.5 mmol), in 2 mL of dry Et_2O, was added under stirring. After 30 min, aqueous NH_4Cl/NH_3 solution (4 mL) was added and the mixture extracted once with ethyl acetate (50 mL). The organic layer was washed with water (10 mL), brine (5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a light-yellow oil that was purified by flash chromatography (hexane/ethyl acetate 20/1) to provide **13** as viscous oil (78 mg, yield 70%) as an inseparable 6:1 *trans*/*cis* diastereoisomeric mixture, as shown by NMR spectra. IR ν_{max} ($CHCl_3$)/cm^{-1}: 1713, 1358, 1217, 1110. ^1H NMR (*trans*/*cis* mixture) (δ, $CDCl_3$): 2.68 (C*H*, m); 2.38 (C*H*, dt, J=6.6, 11.0 Hz); 2.17 (CH_3CO, s); 2.13 (CH_3CO, s); 1.9–1.3 (10H, m); 1.17 (CH_3CH, d, J=6.6 Hz); 1.08 (2×CH_3, s); 1.06 (CH_3, s), 1.02 (CH_3, s); 0.87 (CH_3CH, d, J=6.6 Hz). ^{13}C NMR (*trans*/*cis* mixture) (δ, $CDCl_3$): (*trans*) 211.2 (C=O); 139.9, 127.2 (Cquat); 53.4; 40.4; 34.6; 31.0; 29.9; 29.9; 29.6; 28.4; 23.0; (*cis*) 210.3; 137.1, 127.0 (C quat); 54.8; 40.7; 33.9; 31.3; 29.4; 27.9; 27.6; 23.0. HRMS calcd for $C_{15}H_{24}O$ $[M+NH_4]^+$ 238.1827, found 238.1825.

Method b. To a cold (−78 °C) solution of dimethyl lithium cuprate (2.0 mmol) in 5 mL of dry ether, freshly distilled

trimethylchlorosilane (0.25 mL, 2.0 mmol) was added dropwise under stirring. After 1 h, **10** (102 mg, 0.5 mmol), in 2 mL of dry Et_2O, was added under stirring. After 1 h, the reaction mixture was allowed to warm up to room temperature. The usual work up as previously described furnished 88 mg of **13** (yield 80%) as an inseparable 3:1 *trans*/*cis* diastereoisomeric mixture.

In both methods, the formation of **12** as viscous oil and as a side product derived from 1,2-addition was detected, with a variable yield (method a: 24%; method b: 15%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 3370, 1660, 1358, 1110. ^1H NMR (δ, $CDCl_3$): 5.93 (1H, s), 2.25–1.95 (6H, m), 1.70–1.40 (4H, m), 1.42 (6H, s), 1.08 (6H, s). ^{13}C NMR (δ, $CDCl_3$): 138.9, 134.2, 128.4 (Cquat), 120.2, 77.0 (Cquat), 39.4; 32.2; 31.3; 29.7; 28.1; 25.2; 22.1; 19.7. HRMS calcd for $C_{15}H_{24}O$ $[M+NH_4]^+$ 238.1827, found 238.1830.

4.1.6. 1-[4-Methyl-4-(4-methyl-3-pentenyl)-1-cyclohexenyl]ethan-1-one, 15. Compound **11** (102 mg, 0.5 mmol), under the same reaction conditions and purification to prepare **13** (method a), gave **15** as oil (72 mg, yield 65%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 1685, 1660, 1358, 1210, 1111. ^1H NMR (δ, $CDCl_3$): 6.82 (1H, m); 5.08 (1H, m); 2.28 (3H, s); 2.23 (1H, m); 2.04 (2H, m); 1.95 (2H, m); 1.67 (3H, s); 1.59 (3H, s); 1.42 (2H, m); 1.24 (2H, m); 0.88 (3H, s). ^{13}C NMR (δ, $CDCl_3$): 193.0 (C=O); 139.5, 126.4 (Cquat); 124.8; 122.1; 49.0; 43.1; 42.1; 37.3; 32.8; 27.5; 25.8; 21.9; 17.8. HRMS calcd for $C_{15}H_{24}O$ $[M+NH_4]^+$ 238.1827, found 238.1825.

4.1.7. (+,−)-1-[(1*R,2*S**)-1,2,3,4,5,6,7,8-Octahydro-1,2,8,8-tetramethylnaphthalen-2-yl]ethan-1-one, *Georgywood*, 3.** A *trans*/*cis* mixture of **13** (160 mg, 0.72 mmol) was dissolved in dry THF (10 mL) under argon at 0 °C, then NaH (70 mg, 2.9 mmol) and CH_3I (750 mg, 5.28 mmol) were added. The reaction mixture was allowed to warm up to room temperature, then to reflux for 48 h. The reaction mixture, diluted with Et_2O (50 mL), was treated with MeOH (0.5 mL), then washed, water (5 mL) until neutrality, brine (3 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated in vacuum and the product was purified by flash chromatography (hexane/ethyl acetate 20/1) to give the fragrant oil, *Georgywood*, **3**, as viscous oil and as only one diastereoisomer (101 mg, yield 60%). IR ν_{max} ($CHCl_3$)/cm^{-1}: 2928, 2832, 1702, 1459, 1376, 1357, 1239, 1219, 1195, 1126, 1090, 1065, 1028, 964. ^1H NMR (δ, $CDCl_3$): 2.36 (1H, q); 2.15 (3H, s); 2.1–1.7 (6H, m); 1.55–1.4 (4H, m); 1.06 (3H, s); 1.02 (3H, s); 0.99 (3H, s); 0.86 (3H, d, J=6.6 Hz). ^{13}C NMR (δ, $CDCl_3$): 214.4 (C=O); 136.9, 125.9 (C=C); 50.7 (C2 q); 40.1; 35.4 (C1); 34.0 (C8 q); 30.8; 29.4, 28.4 (CH_3); 27.6; 24.8 (CH_3); 22.5; 21.0, 19.7 (CH_3); 19.1. HRMS calcd for $C_{16}H_{26}O$ $[M+NH_4]^+$ 252.1984, found 252.1988.

Acknowledgements

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Asymmetric oxidopyrylium-alkene [5+2] cycloaddition: a divergent approach for the synthesis of enantiopure oxabicyclo[5.4.0]undecanes☆,☆☆

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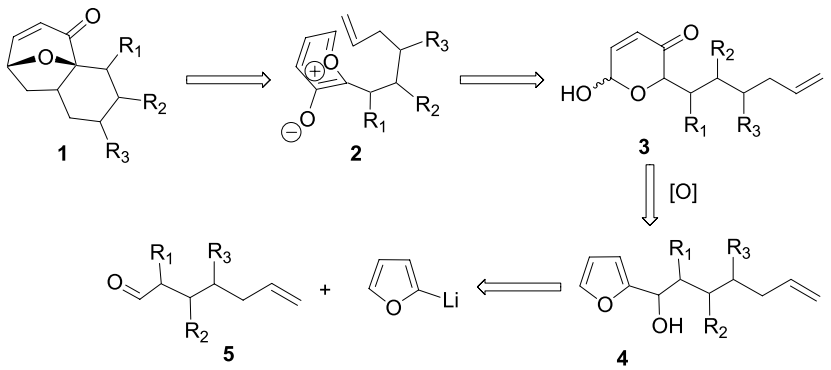
Abstract—A Chiron approach to the synthesis of enantiomeric oxabicyclic adducts **16** and **32** has been developed employing an intramolecular [5+2] cycloaddition of 3-oxidopyrylium with unsaturated sugars.

1. Introduction

3-Oxidopyrylium-alkene [5+2] cycloaddition provides an interesting and potentially versatile entry into highly functionalized oxabicyclo[3.2.1]octane frameworks from simple precursors. The rapid generation of molecular complexity in a relatively easy manner, has made this approach a highly useful tool in the synthesis of seven-membered ring containing complex natural products. Notably, Wender and coworkers have successfully applied this strategy, in an intramolecular fashion, to the total synthesis of natural products phorbol and resiniferatoxin.[1,2] However, compared to other cycloaddition strategies, one of the most important aspects that have received relatively little attention in an efficient [5+2] annulation method, is the asymmetric version of the cycloaddition reaction, despite numerous applications of this class of reactions in organic synthesis. Taking into account the various approaches reported in the literature in this context,[3] we embarked on the development of novel routes to access chiral oxabicyclo adducts. We wish to report here a chiral pool approach for the asymmetric synthesis of oxabicyclic adducts. We demonstrate that the reactions of optically active unsaturated aldehydes derivable from the appropriate sugar derivatives, with 2-lithiofuran provides useful 2-furyl-carbinol intermediates and suitable manipulations of these systems lead to a convenient and flexible route to the asymmetric synthesis of oxabicyclo[m.n.0]adducts. We also



Scheme 1.

☆ CDRI Communication No. 6414.

☆☆ Supplementary data associated with this article can be found in the online version, at doi: 10.1016/j.tet.2004.04.003

Keywords: D-Ribose; 3-Oxidopyrylium; Asymmetric synthesis; [5+2] Cycloaddition.
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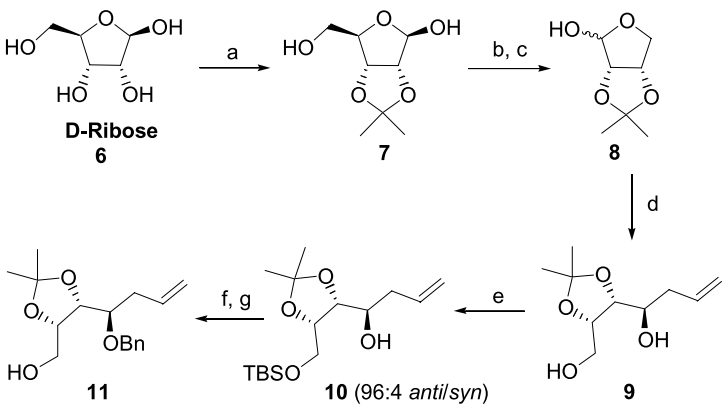


Scheme 2. (a) Me_2CO, H_2SO_4 (cat); (b) $NaBH_4$, MeOH, 2 h; (c) $NaIO_4$, H_2O, 84% (3 steps); (d) allylMgBr, −78 °C; (e) TBDMSCl, imidazole, THF, 72% (2 steps); (f) NaH, BnBr, THF, 0 °C; (g) Bu_4NF, THF, rt, 2 h.

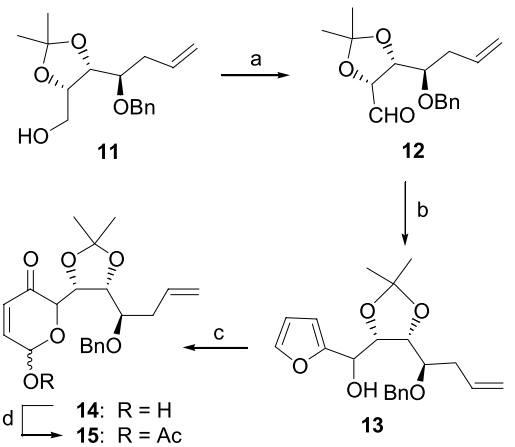
demonstrate that exploitation of the *pseudo*-symmetry of chosen sugar starting material, leads to the synthesis of the enantiomeric partners of the oxabicyclic adducts.[4]

2. Results and discussion

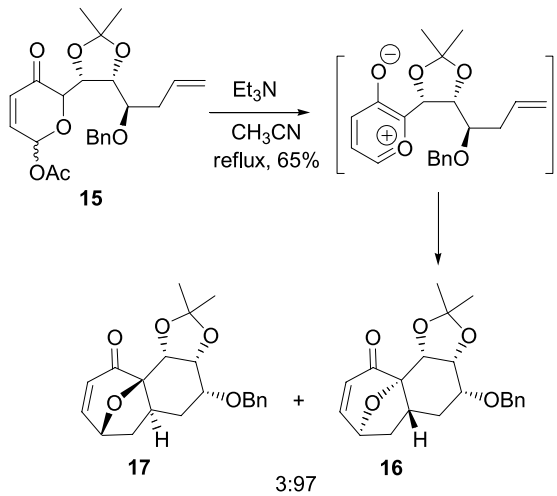
We devised a strategy with an expectation of preparing the optically active oxabicyclo[5.4.0]undecanes. Our approach involves the synthesis of cycloadduct of general type **1** by intramolecular cycloaddition of the 3-oxidopyrylium **2** with the tethered olefin. The pyrylium species **2** could be obtained from the acetoxypyranone **3**, which in turn could be obtained from the 2-furylcarbinol **4**, with requisite stereogenic centers within the tether joining the reacting partners. The synthesis of furylcarbinol (**4**) could be possible by the reaction of 2-lithiofuran with the unsaturated aldehyde **5** (Scheme 1).

The importance of carbohydrates as versatile sources of chiral information in the asymmetric synthesis of various complex organic molecules is well recognized.[5] Our initial efforts were focused on the synthesis of optically active unsaturated aldehydes from the appropriate sugar starting material. After scrutinizing various cheap and commercially available carbohydrates, we chose ribose for our purpose. Isopropylidenation of D-ribose **6** with acetone in the presence of catalytic amount of sulfuric acid gave 2,3-*O*-isopropylidene-D-ribose **7**. Compound **7** on reduction with sodium borohydride afforded the triol, which on oxidative cleavage with sodium periodate ($NaIO_4$) gave 2,3-*O*-isopropylidene-L-erythrose **8** in 84% yield from **7** (Scheme 2).[6] Grignard reaction of compound **8**, using allylmagnesium bromide at −78 °C, afforded the diol **9**. Selective monoprotection of primary alcohol (TBDMSCl/imid.) in **9** provided the compound **10** in 72% yield over 2 steps. The diastereomers (96:4, *anti*/*syn*) were separated by column chromatography and the major isomer was carried forward. The secondary hydroxyl group in **10** was protected as benzyl ether using BnBr/NaH in THF/DMF (4:1) and removal of the TBS group using tetrabutylammonium fluoride (TBAF) afforded the aldehyde precursor **11**.

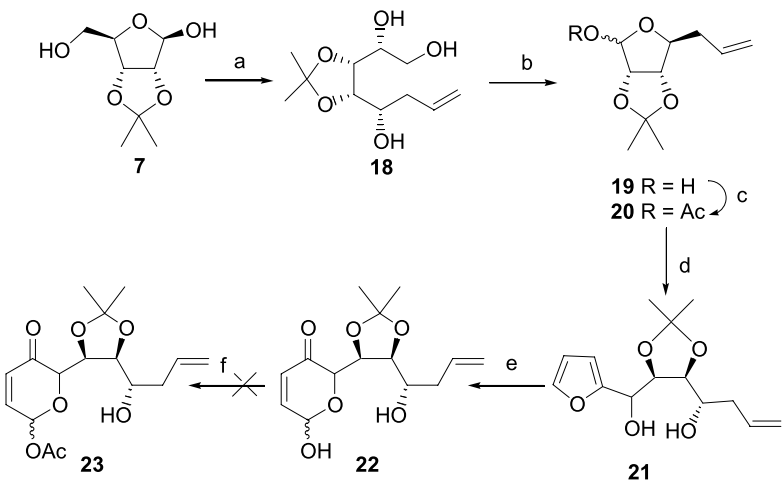
Swern oxidation of alcohol **11** furnished the corresponding aldehyde **12**. Addition of 2-lithiofuran (generated in situ by treating furan with *n*-BuLi at 0 °C) to aldehyde **12** at −78 °C afforded the furylcarbinol **13** (Scheme 3). Oxidative rearrangement of **13** using $VO(acac)_2$/*t*-BuOOH[7] in CH_2Cl_2 gave the hydroxypyranone **14** and acetylation of the anomeric hydroxyl gave the acetoxypyranone **15** in 88% yield from **13**. Oxidopyrylyum-alkene cycloaddition occurred upon treatment of the acetoxypyranone (**15**) with Et_3N (4 equiv.) in CH_3CN under reflux, affording the



Scheme 3. (a) $(COCl)_2$, DMSO, Et_3N, −78 °C; (b) *n*-BuLi, furan, THF, −78 °C, 70%; (c) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 88% (2 steps).



Scheme 4.

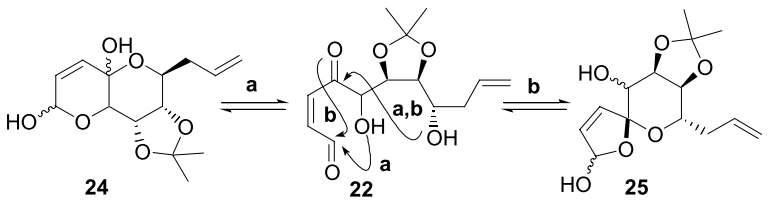


Scheme 5. (a) Diallylzinc, Et_2O, 0 °C, 5 h; (b) $NaIO_4$, water, 85% (2 steps); (c) Ac_2O, pyridine, CH_2Cl_2, 0 °C, 92%; (d) *n*-BuLi, furan, THF, −78 °C, 85%; (e) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, rt, 3.5 h; (f) Ac_2O, pyridine, CH_2Cl_2.

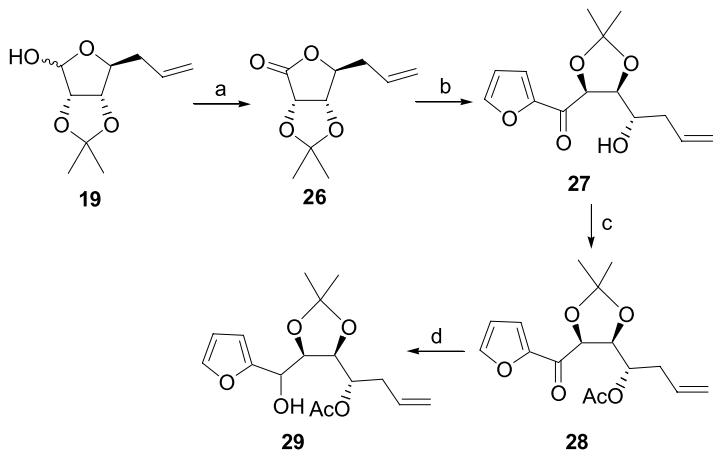
cycloadducts **16** and **17** as an inseparable mixture of diastereomers (93:7, ^{1}H NMR) in 65% yield (Scheme 4). The observed diastereoselectivity of the reaction is in accordance with that reported, which is attributed to the stereogenic center present on the tether, next to the pyrylium moiety.[1b,e,3d]

In order to synthesize other stereo-analogous [5+2] cycloadducts, we decided to exploit the *pseudo*-symmetry of ribose. It was envisioned that the introduction of the furyl unit on the lactol **19** (Scheme 5) would provide us an intermediate which facilitates the reversal of the sense of the asymmetric induction as compared to our previous intramolecular cycloaddition. Accordingly 2,3-*O*-isopropylidine-D-ribose **7** was transformed to the lactol **19** by addition of diallylzinc to **7** (diastereoselectivity 96:4 *anti*/*syn*), followed by sodium periodate cleavage of the resultant triol **18**.[8] Addition of 2-lithiofuran to the lactol **19** yielded the furylcarbinol **21**, which was then oxidatively rearranged to the hydroxypyranone **22**. However, our attempts to transform the pyranone **22** to the corresponding pyrylium ylide precursor (acetoxypyranone) (**23**), were unsuccessful. The reaction resulted in the formation of a complex mixture, which is presumably due to existence of the hydroxypyranone in the form of hemiketals (**24**) and/or spiroketals (**25**) (Scheme 6).[9]

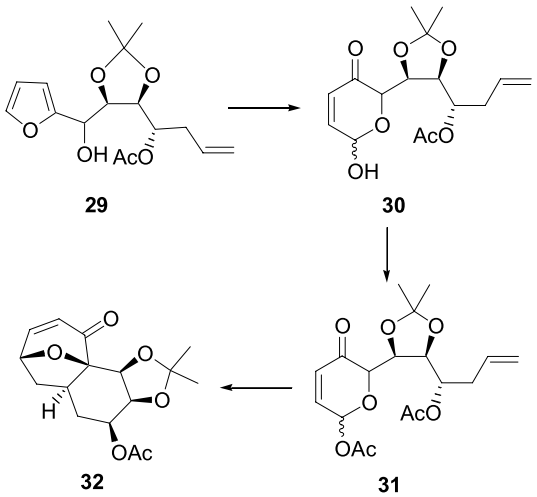
In the light of these results we have modified our synthetic strategy, which is outlined in Scheme 7. The lactol **19** was oxidized to the lactone **26** by Swern oxidation conditions.



Scheme 6.



Scheme 7. (a) $(COCl)_2$, DMSO, Et_3N, −78 °C, 90%; (b) *n*-BuLi, furan, THF, −78 °C, 6 h, 75%; (c) AcCl, pyridine, CH_2Cl_2, 0 °C-rt, 96%; (d) $NaBH_4$, MeOH, 0 °C, 93%.



Scheme 8. (a) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2; (b) Ac_2O, pyridine, DMAP, 0 °C; (c) Et_3N, CH_3CN, reflux, 83%.

Reaction of 2-lithiofuran on lactone **26** at −78 °C for 6 h afforded the monoaddition product **27** in 75% yield. The hydroxyl group in **27** was protected as acetate (AcCl/py), and the keto group was reduced with sodium borohydride to give compound **29** in 89% yield. Oxidative ring expansion of **29** using $VO(acac)_2$/*t*-BuOOH generated the pyranone **30** (Scheme 8). The pyranone **30** was transformed to the acetoxypyranone **31**, which upon treatment with Et_3N in CH_3CN under reflux conditions smoothly underwent highly diastereoselective cycloaddition to yield the cycloadduct **32** (83% yield) and the stereochemistry was unambiguously established by single-crystal X-ray analysis (Fig. 1).

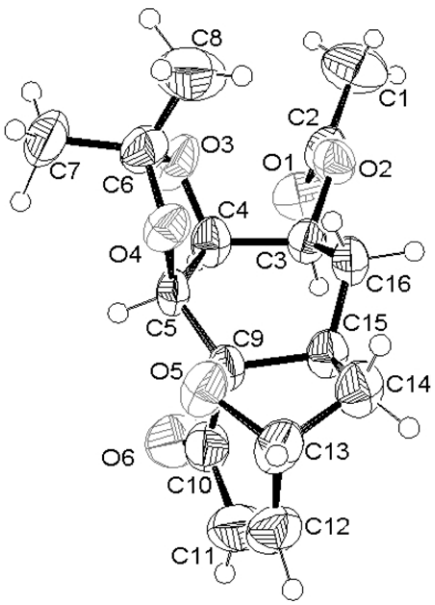


Figure 1. ORTEP drawing of the X-ray structure of **32**.

3. Conclusion

In summary, the synthesis of optically active oxabicyclo-[5.4.0]undecanes have been accomplished using D-ribose as a Chiron for asymmetric induction. We have observed that the cycloadducts **16** and **32** are *pseudo* enantiomers, having variation in the hydroxyl protection groups

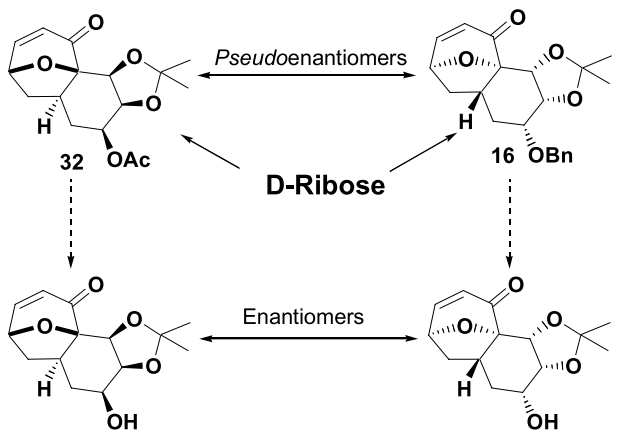


Figure 2.

(OBn, OAc), with diverse functionality around the ring (Fig. 2).

The presence of enone groups in the cycloadducts would permit introduction of other functional groups in stereocontrolled fashion by virtue of their rigid molecular architecture. It seems reasonable to believe that by choosing an appropriate sugar and its suitable manipulations the methodology might find applicability in the synthesis of various important natural products.

4. Experimental

4.1. X-ray diffraction data of 32

Crystals of **32** were obtained by slow evaporation of a solution of **32** in a mixture of petroleum ether and ethyl acetate at room temperature.

Chemical formula: $C_{16}H_{20}O_6$; formula weight: 308.32; crystal system: monoclinic; unit cell dimensions and volume with estimated standard deviations: a: 9.5590(6) Å; b=8.8780(9) Å; c=10.2790(7) Å; α: 90°; β: 114.082(5)°; γ: 90°; volume: 796.40(11) Å^3; temperature 293(2) K; space group $P2_1$; number of molecules in the unit cell (Z): 2; wavelength of radiation (λ): 0.70930 Å; linear absorption coefficient (μ): 0.098 mm^{-1}; number of reflections measured: 1311; number of independent reflections: 1311 [R_{int}=0.0000]; final R indices [$I>2\sigma(I)$]: $R1$=0.0404, $wR2$=0.0880. Crystallographic data (excluding structure factors) for the structure **32** in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC-212708. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Materials and general experimental procedures

The following general procedures were used in all reactions unless otherwise noted. Oxygen- and moisture-sensitive reactions were carried out in flame-dried glassware sealed with a rubber septum under a positive pressure of dry nitrogen or argon. Sensitive liquids and solutions were transferred by syringe or cannula through rubber septa

through which a positive pressure of nitrogen was maintained. THF and Et_2O were distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride, acetonitrile and triethylamine were distilled from calcium hydride. Pyridine was refluxed over KOH pellets and distilled. Melting points were determined with a veego apparatus of Buchi type and are uncorrected. NMR spectra were measured in a Fourier transform mode on a Varian mercury-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), and Varian VXR-300s (^{1}H at 300 MHz, ^{13}C at 75 MHz) magnetic resonance spectrometer. Infrared spectra were recorded on a Nicolet Impact 400 and Thermo Nicolet Avatar 320 series Fourier transform spectrometer (FTIR) and are reported in wavenumbers (cm^{-1}). Optical rotations were determined with a JASCO DIP-370 digital polarimeter at ambient temperature.

4.2.1. 1-(5-Hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-but-3-en-1-ol (9). A dry, 100 ml, three-necked, round-bottomed flask is charged with excess of Mg (1.8 g, 0.075 g-atom) and 40 ml anhydrous Et_2O. To the stirred mixture was added dropwise a solution of allyl bromide (7.4 g, 5.3 ml, 61 mmol) in 61 ml of Et_2O at such a rate to maintain gentle reflux. After the addition is over the mixture was refluxed for 30 min. To this a solution of **8** (0.974 g, 6.1 mmol) in ether (20 ml) at −78 °C was added dropwise. The resulting mixture was stirred for 1 h at −78 °C and then allowed to warm to room temperature over 4 h. The reaction mixture was quenched by adding cold saturated NH_4Cl (100 ml) and extracted with ethyl acetate. The organic phase was washed with brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. The crude mixture can be used directly in the next step.

$[\alpha]_D^{25}$=+51.7 (*c* 0.6, $CHCl_3$). IR (neat) ν_{max} 3422, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.89–5.82 (m, 1H), 5.22–5.18 (m, 2H), 4.34–4.30 (m, 1H), 4.0–3.96 (m, 1H), 3.89–3.76 (m, 3H), 2.85 (br s, 1H), 2.61 (m, 2H), 2.20 (m, 1H), 1.41 (s, 3H), 1.35 (s, 3H).

HRMS (EI) calculated for $C_{10}H_{18}O_5$: 202.1205 (M^+), found 202.1205.

4.2.2. 1-[5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-3-en-1-ol (10). To the solution of the diol **9** (0.5 g, 2.5 mmol) in THF/DMF (3:1, 5 ml) at 0 °C was added TBDMSCl (0.45 g, 2.9 mmol) and imidazole (0.43 g, 6.25 mmol). After 1 h, the mixture was poured into ether and the ether layer was washed with water, saturated $NaHCO_3$, and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the diastereomers **10** (*anti*/*syn* 96:4) in 72% yield over 2 steps.

anti Isomer: $[\alpha]_D^{25}$=−8.3 (*c* 0.6, $CHCl_3$).

IR (neat) ν_{max} 3420, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.19–5.91 (m, 1H), 5.18–5.07 (m, 2H), 4.25–4.18 (m, 1H), 4.09–4.04 (m, 1H), 3.89–3.75 (m, 3H), 3.60–3.56 (m, 1H), 2.53–2.51 (m, 1H), 2.29–2.24 (m, 1H), 1.36 (s, 3H), 1.32 (s, 3H), 0.89 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H).

HRMS (FAB) calculated for $C_{16}H_{32}O_4SiNa$: 339.1968 (MNa^+), found 339.1975.

syn Isomer: $[\alpha]_D^{25}$=+8.9 (*c* 0.56, $CHCl_3$).

IR (neat) ν_{max} 3420, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92–5.83 (m, 1H), 5.18–5.10 (m, 2H), 4.18–4.13 (m, 1H), 4.09–4.06 (m, 1H), 3.95–3.86 (m, 2H), 3.76–3.71 (m, 1H), 2.87–2.86 (d, *J*=5.1 Hz, 1H), 2.37 (m, 2H), 1.48 (s, 3H), 1.37 (s, 3H), 0.90 (s, 9H), 0.10 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 135.0, 117.4, 108.1, 78.9, 77.3, 68.5, 61.9, 39.0, 27.4, 25.9, 25.2, 18.4, −5.3.

4.2.3. [5-(1-Benzyloxy-but-3-enyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-methanol (11). To a solution of *anti*-isomer **10** (0.3 g, 0.95 mmol) in THF (5 ml) at 0 °C was added NaH (60 mg, 60%) and benzyl bromide (0.2 ml) and the resulting mixture was stirred for 3 h. The reaction mixture was quenched by addition of saturated NH_4Cl and extracted with ether. The organic phase was washed with water, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the product.

$[\alpha]_D^{25}$=−15.7(*c* 0.83, $CHCl_3$).

IR (neat) ν_{max} 3420, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.38–7.30 (m, 5H), 5.98–5.94 (m, 1H), 5.20 (m, 2H), 4.65 (d, *J*=11.1 Hz, AB system, 1H), 4.44 (d, *J*=11.1 Hz, AB system, 1H) 4.23–4.12 (m, 2H), 3.90 (dd, *J*=3.6, 11 Hz, 1H), 3.79–3.68 (m, 2H), 2.63–2.40 (m, 2H), 1.46 (s, 3H), 1.35 (s, 3H), 0.95 (s, 9H), 0.89 (s, 6H).

To this compound in THF (13 ml) at 0 °C was added *n*-Bu_4NF (0.75 ml, 1 M in THF, 0.75 mmol). After being stirred for 2 h at room temperature, water (10 ml) was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the desired product **11** (0.174 g, 63% in 2 steps).

$[\alpha]_D^{25}$=−41.3° (*c* 0.63, $CHCl_3$).

IR (neat) ν_{max} 3425, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34–7.30 (m, 5H), 6.0–5.89 (m, 1H), 5.23–5.14 (m, 2H), 4.71 (d, *J*=11 Hz, AB system, 1H), 4.45 (d, *J*=11 Hz, AB system, 1H), 4.30 (dd, *J*=6, 11.7 Hz 1H), 4.15 (dd, *J*=6, 8.7 Hz, 1H), 3.79 (m, 1H),

3.70 (br m, 2H), 2.65 (m, 1H), 2.51 (m, 2H), 1.45 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.3, 133.2, 128.7, 128.2, 118.3, 108.3, 77.5, 76.3, 71.3, 61.2, 34.2, 28.0, 25.5.

HRMS (FAB) calculated for $C_{17}H_{24}O_4Na$: 315.1573 (MNa^+), found 315.1567.

4.2.4. [5-(1-Benzyloxy-but-3-enyl)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-furan-2-yl-methanol (13). To a solution of oxalyl chloride (0.044 ml, 0.63 mmol) in CH_2Cl_2 (1 ml) at −78 °C was added dropwise a solution of DMSO (0.094 ml, 1.26 mmol) in CH_2Cl_2 (0.5 ml). After 5 min, a solution of the alcohol **11** (0.14 g, 0.48 mmol) in CH_2Cl_2 (1 ml) was added. Stirring was continued for 20 min at −78 °C and Et_3N (0.33 ml, 2.39 mmol) was added dropwise. The resulting mixture was slowly allowed to warm to room temperature and stirred for 1 h. Water (5 ml) was added, and the organic layer was separated and concentrated under reduced pressure. The residue was diluted with ether (50 ml) and washed with water, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure to give the crude aldehyde **12** (0.139 g), which was immediately used in the next step without further purification.

In a different flask, a solution of furan (0.33 ml, 4.32 mmol, freshly distilled over KOH) in THF (2.86 ml) was added dropwise a solution of *n*-BuLi (0.7 ml, 15% in hexane, 2.3 mmol) at −78 °C. After stirring for 3 h at 0 °C under argon, the mixture was cooled to −78 °C and a solution of aldehyde **12** (0.139 mg, 0.479 mmol) in THF (1 ml) was added dropwise. The resulting mixture was stirred for 3 h before being quenched by addition of saturated NH_4Cl solution (5 ml). The organic layer was separated and the aqueous layer was extracted with ether. The combined organic phases were washed with brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the desired compound **13** (0.86 g, 70%) as yellow oil.

$[\alpha]_D^{25}=-97°$ (*c* 0.33, $CHCl_3$).

IR (neat) ν_{max} 3460, 1645 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35–7.25 (m, 6H), 6.30 (m, 2H), 5.94 (m, 1H), 5.2 (m, 2H), 4.92 (dd, *J*=7.6, 2.4 Hz, 1H), 4.67 (d, *J*=11.2 Hz, AB system, 1H), 4.5 (m, 1H), 4.40 (d, *J*=10.8 Hz, AB system, 1H), 4.26 (m, 1H), 4.06 (m, 1H), 2.92 (d, *J*=7.6 Hz, 1H), 2.67 (m, 1H), 2.5 (m, 1H), 1.54 (s, 3H), 1.37 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.9, 141.9, 137.8, 133.4, 128.8, 128.6, 128.5, 127.9, 127.8, 118.1, 110.3, 108.4, 106.9, 77.9, 77.5, 76.7, 71.1, 65.8, 34.6, 26.9, 24.7.

4.2.5. Synthesis of cycloadducts 16 and 17. To a solution of furylcarbinol **13** (0.48 g, 0.134 mmol) in dry CH_2Cl_2 (1 ml) at −20 °C was added *t*-BuOOH (0.03 ml) and $VO(acac)_2$ (1.69 mg, 0.008 mmol)) under argon atmosphere. The resulting dark solution was stirred at −20 °C for 1 h and then at room temperature for 3 h. The pale yellow solution was diluted with CH_2Cl_2, washed with water brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure (ν_{max} 3415, 1694, 1639 cm^{-1}). The resultant residue was taken in CH_2Cl_2 (2 ml) containing pyridine (0.06 ml) at 0 °C, and treated with acetic anhydride (0.24 ml) and 4-dimethylaminopyridine (DMAP) (catalytic). The resulting mixture was stirred for 1 h at 0 °C. CH_2Cl_2 was added and the organic layer was treated with 5% hydrochloric acid, saturated $NaHCO_3$, water and dried over Na_2SO_4. Evaporation of the solvent followed by flash column chromatography afforded the desired compound **15** in quantitative yield. This crude material was used as such in the next step.

IR (neat) ν_{max} 1749, 1701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33–7.25 (m, 5H), 6.90 (dd, *J*=10, 3.6 Hz, 1H), 6.58 (d, *J*=3.6 Hz, 1H), 6.22 (d, *J*=10 Hz, 1H), 5.72 (m, 1H), 5.15 (m, 2H), 4.88 (d, *J*=6.4 Hz, 1H), 4.74 (m, 2H), 4.35 (m, 2H), 4.0 (m, 1H), 2.76 (m, 1H), 2.45 (m, 1H), 2.1 (s, 3H), 1.32 (s, 3H), 1.25 (s, 3H).

To a solution of pyranone acetate **15** (0.38 g, 0.09 mmol) in CH_3CN (0.5 ml) was added Et_3N (0.005 ml) at room temperature. The reaction mixture was heated at reflux for 20 h. After being cooled to 25 °C, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the cycloadduct **16** and **17** as 93:7 inseparable mixtures of diastereomers in 65% yield.

$[\alpha]_D^{25}=+38.5°$ (*c* 0.91, $CHCl_3$). IR (neat) ν_{max} 1693 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.4–7.2 (m, 5H), 7.2 (dd, *J*=9.6, 4.4 Hz, 1H), 5.9 (d, *J*=9.6 Hz, 1H), 5.0 (d, *J*=6.8 Hz, 1H), 4.9 (m, 1H), 4.70 (d, *J*=12 Hz, AB system, 1H), 4.59 (d, *J*=12.4 Hz, AB system, 1H), 4.65 (m, 1H), 3.40 (m, 1H), 1.9–1.7 (m, 5H), 1.4 (s, 3H), 1.3 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 197.0, 152.3, 138.0, 128.3, 127.6, 127.5, 125.5, 109.6, 84.1, 75.1, 72.9, 72.6, 70.6, 38.5, 35.5, 28.2, 26.3, 24.9.

HRMS (EI) calculated for $C_{21}H_{25}O_5$: 356.1624 (M^+), found 356.1628.

4.2.6. 6-Allyl-2,2-dimethyl-dihydro-furo[3,4-*d*][1,3]-dioxol-4-one (26). To a solution of oxalyl chloride (1.56 ml, 17.94 mmol) in CH_2Cl_2 (40 ml) at −78 °C was added dropwise a solution of DMSO (3.12 ml, 44.1 mmol) in CH_2Cl_2 (14 ml). (3.13 g, 15.63 mmol). After 5 min, a solution of the lactol **19**[8] in CH_2Cl_2 (24 ml) was added. Stirring was continued for 20 min at −78 °C and Et_3N (11.5 ml) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. Water (25 ml) was added, and the organic layer was separated and concentrated under reduced pressure. The residue was diluted with ether (50 ml) and washed with water, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the lactone **26** (2.8 g, 90%) as oil.

$[\alpha]_D^{25}$=+52.5° (*c* 0.4, $CHCl_3$).

IR (neat) ν_{max} 3446, 1785, 1641 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 5.76–5.69 (m, 1H), 5.24 (m, 2H), 4.71 (d, *J*=6.1 Hz, 1H), 4.65 (t, *J*=6.1 Hz, 1H), 4.58 (d, *J*=6.1 Hz, 1H), 2.5 (m, 2H), 1.47 (s, 3H), 1.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 130.3, 120.8, 113.7, 81.9, 78.8, 74.9, 37.5, 26.9, 25.8.

HRMS (FAB) calculated for $C_{10}H_{14}NaO_4$: 199.0970 (MNa^+), found 199.0982.

4.2.7. Acetic acid 1-[5-(furan-2-carbonyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-3-enyl ester (28). To a solution of furan (0.29 ml, 3.795 mmol) in ether (8 ml) was added dropwise a solution of *n*-BuLi (1.25 ml, 15% in hexane) at −78 °C. After stirring for 3 h at 0 °C under argon, the mixture was cooled to −78 °C and a solution of lactone **26** (0.5 g, 2.53 mmol) in ether (10 ml) was added dropwise. The resulting mixture was stirred at −78 °C for 6 h before being quenched by addition of methanol (1 ml). After warming to room temperature the solution was extracted with ether. The organic phases were washed with NH_4Cl and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure to afford the furyl ketone **27** along with some amount of unreacted lactone **26**. This mixture was difficult to separate by column chromatography and hence it was carried through the next step.

To a solution of **26** (0.25 g, 0.94 mmol) in dry CH_2Cl_2 (4 ml) at 0 °C was added pyridine (0.27 ml, 3.29 mmol) and freshly distilled acetyl chloride (0.14 ml, 1.9 mmol). The resulting suspension was stirred at 0 °C for 1 h, then warmed to room temperature and stirred for a further 2 h. The reaction was diluted with CH_2Cl_2 and the organic layer was washed with saturated sodium bicarbonate solution, 5% hydrochloric acid, brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification of the resultant residue by flash chromatography afforded the desired product **28** in 72% over 2 steps.

$[\alpha]_D^{25}$=−23.4° (*c* 0.47, $CHCl_3$).

IR (neat) ν_{max} 1741, 1685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.61 (d, *J*=1.5 Hz, 1H), 7.36 (d, *J*=3.9 Hz, 1H), 6.55 (dd, *J*=3.9, 1.5 Hz, 1H), 5.74–5.60 (m, 1H), 5.31 (d, *J*=6.9 Hz, 1H), 5.0 (m, 2H), 4.79 (m, 1H), 4.61 (m, 1H), 2.5 (m, 1H), 2.3 (m, 1H), 1.7 (s, 3H), 1.68 (s, 3H), 1.43 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 182.5, 168.9, 151.5, 146.7, 132.5, 118.5, 118.2, 112.5, 110.4, 78.7, 77.7, 70.7, 34.7, 27.2, 25.3, 20.5.

HRMS (FAB) calculated for $C_{16}H_{20}NaO_6$: 331.1158 (MNa^+), found 331.1172.

4.2.8. Acetic acid 1-[5-(furan-2-yl-hydroxy-methyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-but-3-enyl ester (29). To a solution of furyl ketone **28** (0.2 g, 0.65 mmol) in MeOH (3 ml) at 0 °C was added sodium borohydride (40 mg, 1.05 mmol). The reaction mixture was stirred at 0 °C for 1 h, and then quenched by addition of water and extracted with CH_2Cl_2. The organic phase was washed with brine and dried over Na_2SO_4, filtered and evaporated. Purification of the resultant residue by flash chromatography afforded the desired adduct **29** (0.193 g, 93%) as yellow oil.

$[\alpha]_D^{25}$=41.2° (*c* 0.34, $CHCl_3$).

IR (neat) ν_{max} 3466, 1737, 1641 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$) δ: 7.41 (s, 1H), 6.34 (m, 2H), 5.98–5.74 (m, 1H), 5.27–5.07 (m, 3H), 4.7 (d, *J*=8.4 Hz, 1H), 4.5 (m, 1H), 4.43 (m, 1H), 2.5 (m, 1H), 2.3–2.2 (m, 2H), 2.1 (s, 3H), 1.4 (s, 3H), 1.3 (s, 3H).

^{13}C NMR: (75 MHz, $CDCl_3$) δ: 170.0, 153.8, 142.2, 132.8, 118.1, 110.2, 108.6, 107.9, 78.0, 76.9, 70.4, 65.7, 35.9, 27.6, 25.4, 21.2.

HRMS (FAB) calculated for $C_{16}H_{23}O_6$: 311.1494 (MH^+), found 311.1511.

4.2.9. Synthesis of cycloadduct 32. To a solution of furylmethanol **29** (0.1 g, 0.32 mmol) in dry CH_2Cl_2 (2.4 ml) at −20 °C was added *t*-BuOOH (0.074 ml) and $VO(acac)_2$ (2.69 mg, 0.012 mmol) under argon atmosphere. The resulting dark solution was stirred at −20 °C for 1 h and then at room temperature for 3 h. The pale yellow solution was diluted with CH_2Cl_2, washed with water brine and dried over Na_2SO_4. The crude reaction mixture was filtered and concentrated under reduced pressure (ν_{max} 3453, 1738, 1702, 1641 cm^{-1}). The resultant residue was (0.135 g, 0.41 mmol) was taken in CH_2Cl_2 (2 ml) containing pyridine (0.07 ml, 0.85 mmol) at 0 °C, was treated with acetic anhydride (0.47 ml) and 4-dimethylaminopyridine (catalytic). The resulting mixture was stirred for 1 h at 0 °C. CH_2Cl_2 was added and the organic layer was treated with 5% hydrochloric acid, saturated $NaHCO_3$, water and dried over Na_2SO_4. Evaporation of the solvent followed by flash column chromatography afforded the desired compound **31** (ν_{max} 1738, 1699, 1647 cm^{-1}) which was carried to the next step without further purification.

To a solution of pyranone acetate **31** (0.1 g, 0.27 mmol) in CH_3CN (1.5 ml) was added Et_3N (0.05 ml) at room temperature. The reaction mixture was heated at reflux for 6 h. after being cooled to 25 °C, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography to afford the cycloadduct **32** (0.70 g, 83%).

$[\alpha]_D^{25}$=−183.3° (*c* 0.42, $CHCl_3$).

IR ($CHCl_3$) ν_{max} 1738, 1693 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ: 7.22 (dd, *J*=9.6, 4 Hz, 1H), 5.97 (d, *J*=9.6 Hz, 1H), 5.0 (m, *J*=6.4, 3.2 Hz, 1H), 4.93 (dd, *J*=4.8, 4 Hz, 1H), 4.64 (m, 2H), 2.20–1.87 (m, 5H), 2.1 (s, 3H), 1.56 (s, 3H), 1.40 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.3, 170.0, 151.9, 125.3, 109.6, 109.5, 83.7, 72.9, 72.8, 72.0, 70.6, 37.8, 35.3, 27.8, 26.2, 24.9, 21.0.

HRMS (EI) calculated for $C_{16}H_{20}O_6$: 308.1260 (M^+), found 308.1271.

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Dibromomethane as one-carbon source in organic synthesis: a versatile methodology to prepare the cyclic and acyclic α-methylene or α-keto acid derivatives from the corresponding terminal alkenes

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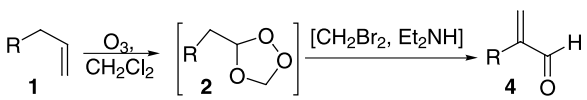
Dedicated to Professor Teh-Chang Chou of National Chung Cheng University on the occasion of his 60th birthday

Abstract—Ozonolysis of mono-substituted alkenes **A**-**1** followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH affords α-substituted acroleins **A**-**2** in good yields. Under very mild reaction conditions, these α-substituted acroleins **A**-**2** can be easily converted to α-methylene esters **A**-**4**, which could be further converted to the corresponding α-keto esters **A**-**5**. This methodology can be also applied to the preparation of α-methylene lactones **B**-**4**, α-methylene lactams, and α-keto lactones **B**-**5** with various ring sizes.

1. Introduction

In the previous studies, the ozonide **2** or aldehyde **3** was treated with a preheated mixture of CH_2Br_2 and Et_2NH to give the acrolein **4** in modest to good yields (Eqs. 1 and 2)[1] whilst the aryl alkyl ketone **5** reacted with a mixture of CH_2Br_2 and Et_2NH under microwave condition to give the corresponding α-methylene ketone **6** (Eq. 3).[2] The β-carbon of the conjugated carbonyl compound was derived from CH_2Br_2. In comparison with similar transformation reported in the literature,[3–5] the characteristic features of our methodology are described as follows. Both CH_2Br_2 and Et_2NH are cheap. Their salts can be easily prepared in situ and used in the same flask to carry out the α-methylenation. The reaction was carried out in nonaqueous media under mild reaction condition. In addition, both ozonide and aldehyde can be converted to the desired product. Therefore, a preheated mixture of CH_2Br_2 and Et_2NH is a convenient and economic reagent as one-carbon synthetic equivalent in organic synthesis.



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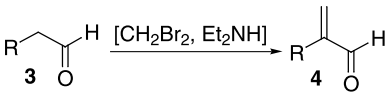

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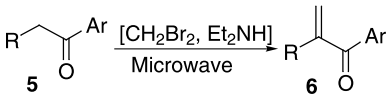

(3)

α-Methylene-γ-butyrolactone is an important moiety in several biological active compounds. Therefore, the development of their preparative methodologies has been attractive to many synthetic organic chemists.[6–19] However, there are only few reports to describe the preparation of α-methylene-β-propiolactones[20,21] and α-methylene-δ-valerolactones.[22,23] To the best of our knowledge, there is no general strategy which can be useful to prepare 4- to 7-memebred ring α-methylene lactones.[24] α-Keto acid derivatives play important roles not only in organic synthesis but also in biologically active natural products.[25,26] The preparation of the α-keto acid was categorized as the following. Oxidation of α-hydroxy esters or their equivalents,[27a–c] oxidative cleavage of the double bond of α,β-unsaturated carbonyl compounds,[27d,e] α-oxidation of carbonyl groups,[27f] and metal-catalyzed double carbonylation[27g] are typical methods to prepare α-keto acid derivatives.[27] Likewise, α-keto amides are mostly obtained from amidation of α-hydroxy esters or acids, followed by oxidation. Of the above methods, most lack generality or suffer from lengthy procedures. The use of toxic KCN and drastic hydrolytic conditions limit the application of some

Keywords: Ozonides; α-Methylenation; α-Substituted acroleins; α-Methylene esters; α-Methylene lactones; α-Methylene lactams; α-Keto esters; α-Keto lactones.
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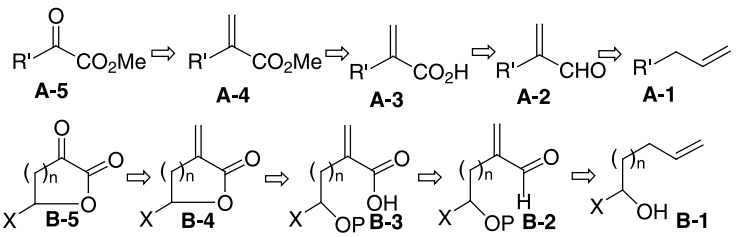


Figure 1. Retrosynthesis of the acyclic and cyclic α-methylene or α-keto carboxylates.

methods for the preparation of α-keto acid derivatives with labile functional groups.[27a–c]

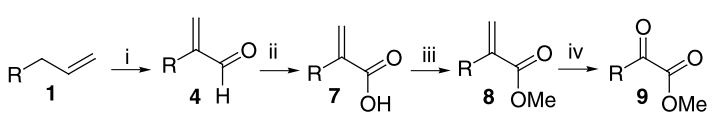
In our previous report, we described a methodology to prepare the α-methylene acid or α-keto acid derivatives from the corresponding terminal alkenes. The α-methylene group is a masked form of carbonyl group. The α-substituted acroleins were proved to be the suitable precursors to the formation of α-keto acid derivatives.[28] Its retrosynthetic analysis was described in Figure 1. The α,β-unsaturated carboxylic acid **A-3** would be prepared from the mild oxidation of the α,β-unsaturated aldehyde **A-2**, which would be derived easily from terminal alkene **A-1** by our reaction condition as shown in Eq. 1. The methyl acrylate **A-4** would be a reasonable precursor to the α-keto acid ester **A-5**. By using similar methodology, the hydroxy-alkene **B-1** would be a reasonable starting material for the preparation of α-methylene lactone **B-4** and α-keto lactone **B-5**. The ring size of the lactone is dependent on the chain length of the spacer between the hydroxy and alkene moieties of compound **B** (Fig. 1). In this report, we shall describe our effort in the synthesis of acyclic and cyclic α-methylene acid derivatives and their α-keto acid derivatives in detail.

2. Results and discussion

2.1. Preparation of acyclic α-methylene acids and their α-keto acid derivatives from the corresponding terminal alkenes

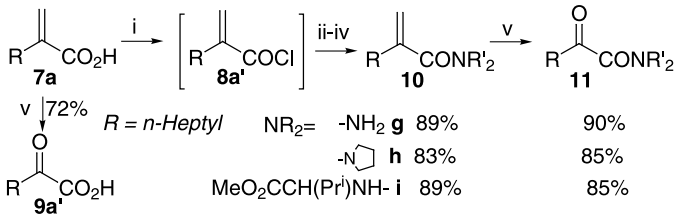
The ozonolysis of 1-decene (**1a**) followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH afforded acrolein **4a** in 62% yield. The oxidation of acroleins to methyl acrylates by MnO_2 in the presence of KCN in methanol has been reported in high yield.[29] In order to avoid using toxic KCN, we tried to use other reagents. The oxidation of α-substituted acrolein **4a** by Jones reagent gave an inseparable mixture of the acrylic acid **7a** in addition to an over-oxidized product. We found that a modified procedure using sodium chlorite in the presence of a chlorine scavenger (i.e, 2-methyl-2-butene) resulted in the acrylic acid **7a** formation in 98% yield.[30] The acrylic acid **7a** was treated with 1 equiv. of diazomethane to give the methyl acrylate **8a** in excellent yield. The presence of excess diazomethane might result in the further 1,3-dipolar cycloaddition to give Δ^1-pyrazoline.[31] In general, the isolation of the acrylic acid **7a** is not necessary before its reaction with diazomethane. The ozonolysis of methyl acrylate **8a** followed by the reduction with Ph_3P afforded α-keto ester **9a** in 69% yield (Scheme 1).

As the reaction conditions involved in Scheme 1 were very mild, it was likely that the sequence might tolerate the presence of the labile groups. Both the keto-olefins **1b**[32] and **1c**[32] can be converted to the α-substituted acroleins **4b** and **4c**, respectively, in good yields where the keto groups remain intact. Moreover, the acrolein **4c**, with the quaternary center adjacent to the α-methylene group, was formed in 61% yield. These acroleins could be converted to α-keto esters **9b** and **9c** in good yields. Hydroxy-olefin **1d**, acetoxy-olefin **1e**, and iodo-olefin **1f** were also transformed into the corresponding α-keto ester derivatives in good yields via similar sequences (Scheme 1). The only exception was that the reducing agent in the ozonolysis of hydroxy-acrylate **8d** was Me_2S rather than Ph_3P. It is because the polarity of α-keto ester **9d** is close to Ph_3PO on silica gel thin layer chromatography. When α-keto ester **9d** was exposed to the silica gel for a long period of time while



R= *n*-Heptyl **a**	62%	98%	98%	69%
b	63%	83%	96%	64%
c	61%	72%	86%	71%
$HO(CH_2)_8$- **d**	64%	85%	91%	62%[v]
$AcO(CH_2)_8$- **e**	63%	98%	87%	69%
$I(CH_2)_8$- **f**	68%	98%	87%	67%

Scheme 1. Reagents and conditions: (i) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv.=5:15); (ii) 2.3 mol equiv. $NaClO_2$, *t*-BuOH, 2 mol equiv. $NaH_2PO_4{\cdot}2H_2O$, 3 mol equiv. $MeCH{=}CMe_2$; (iii) CH_2N_2; (iv) (a) O_3, CH_2Cl_2, −78 °C; (b) 0.7 mol equiv. Ph_3P; (v) (a) O_3, CH_2Cl_2, −78 °C; (b) 1.1 mol equiv. Me_2S.



Scheme 2. Reagents and conditions: (i) 5 mol equiv. $SOCl_2$; (ii) NH_4OH; (iii) pyrrolidine; (iv) 1.1 mol equiv. L-valine methyl ester, 2 mol equiv. Et_3N; (v) O_3, CH_2Cl_2, −78 °C; 0.7 mol equiv. Ph_3P.

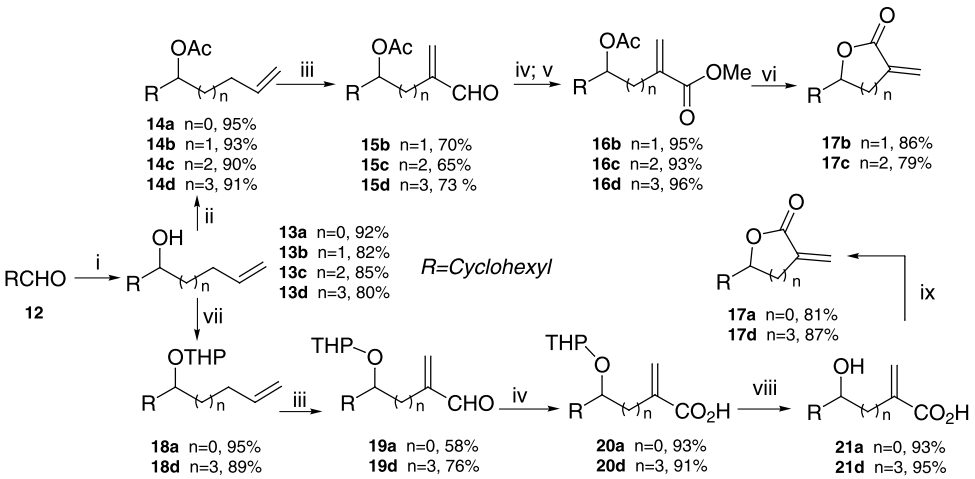
eluting with the lower polarity solvent system, it would result in the dimerization of the α-keto ester **9d**. This obstacle can be overcome by using Me_2S as reducing agent, where the DMSO byproduct is easily removed by extraction.

Acrylic acid **7a** was converted to the acryloyl chloride **8a′** with thionyl chloride in excellent yield. There is no double bond isomerization problem under this acidic condition. The crude acid chloride **8a′** reacted with ammonium hydroxide to give an excellent yield of acrylamide **10g**, which was subjected to the ozonolysis to yield the corresponding α-keto amide **11g** in 90% yield. The acryloyl chloride **8a′** also reacted with pyrrolidine or (±)-valine methyl ester to afford the corresponding acryloyl amides **10h** and **10i** in excellent yields. Under similar conditions, these α-substituted acryloyl amides were also converted to the corresponding α-keto amide **11g**-**11h** in excellent yields. The ozonolysis of acrylic acid **7a** followed by reduction with Ph_3P afforded the α-keto acid **9a′** in 73% yield (Scheme 2). In general, the yield for the formation of α-keto amides is better than that of α-keto esters. Our methodology is suitable to prepare the acyclic α-methylene acid derivatives and their α-keto acid derivatives with labile functional groups.

2.2. Preparation of mono-substituted α-methylene lactones with different ring sizes

The secondary alcohols **13a**-**13d**, prepared from the addition of alkenylmagnesium bromides with cyclohexanecarbaldehyde (**12**), were treated with acetic anhydride to give the acetates **14a**-**14d** in excellent yields (Scheme 3). The ozonolysis of acetoxy-alkene **14a** followed by treatment with a preheated mixture of CH_2Br_2 and Et_2NH in the same flask gave 3-cyclohexylacrolein instead of the desired α-substituted acrolein. Presumably, the elimination of the acetic acid from β-acetoxy aldehyde intermediate is a preferred process. We tried to change the protecting group with less leaving tendency in order to avoid this elimination problem. Under the catalysis of acetonyltriphenylphosphonium bromide (ATPB),[33] the secondary alcohol **13a** reacted with 3,4-dihydro-2*H*-pyran (DHP) to give tetrahydropyranyl ether (OTHP) **18a** in excellent yield. Fortunately, we were able to obtain the acrolein product **19a** in 58% yield by using our standard α-methylenation protocol. The α-substituted acrolein **19a** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently deprotected with ATPB in MeOH[33] to give the corresponding hydroxy-acid **21a**. Compound **21a** was treated with *o*-nitrophenylsulfonyl chloride[34] in the presence of Na_2CO_3 to give β-cyclohexyl-α-methylene-β-propiolactone (**17a**) in excellent yield.

The ozonolysis of acetoxy-alkene **14b** followed by our standard α-methylenation protocol afforded the desired α-methylene aldehyde **15b**, which was subsequently treated with $NaClO_2$ followed by reaction with CH_2N_2 to give methyl acrylate **16b** in excellent yield. The lactonization of the acetoxy-ester **16b** was achieved by treatment with hydrogen chloride, which was generated in situ from the



Scheme 3. Reagents and conditions: (i) $CH_2{=}CH(CH_2)_nMgBr$, THF, −78 °C; (ii) cat. DMAP, pyridine, Ac_2O, CH_2Cl_2; (iii) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol ratio 5:15); (iv) 2.3 mol equiv. $NaClO_2$, *t*-BuOH, 2 mol equiv. NaH_2PO_4-$2H_2O$, 3 mol equiv. $MeCH{=}CMe_2$; (v) CH_2N_2; (vi) cat. AcCl, MeOH; (vii) DHP, cat. ATPB, CH_2Cl_2; (viii) cat. ATPB, MeOH; (ix) *o*-NO_2PhSO_2Cl, Na_2CO_3, CH_2Cl_2.

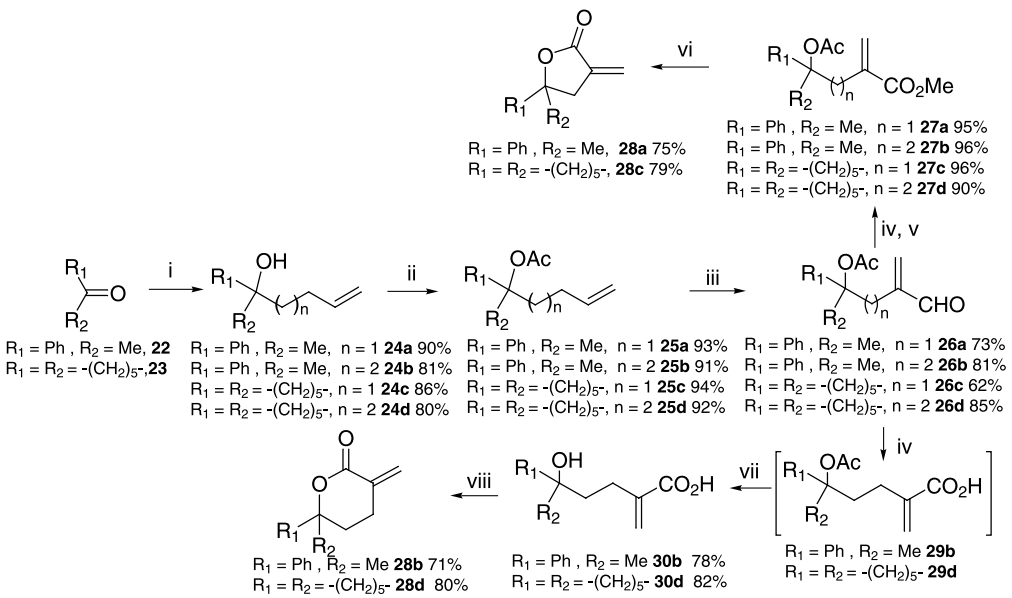
reaction of a catalytic amount of acetyl chloride in the presence of methanol, to give the γ-cyclohexyl-α-methylene-γ-butyrolactone (**17b**) in 86% yield. Following the same reaction sequences, the acetoxy-alkene **14c** was also converted to the δ-cyclohexyl-α-methylene-δ-valerolactone (**17c**) in good yield (Scheme 3).

The acetoxy-acrylate **16d** was prepared in a similar manner in good yield from the acetoxy-alkene **14d** in order to synthesize 7-membered ring α-methylene lactone. Unfortunately, the acetoxy-acrylate **16d** cannot undergo lactonization by treatment with acid methanol (Scheme 3). We isolated the corresponding acyclic hydroxy-ester from the methanolysis of the acetoxy group. However, we did not obtain the lactonization product **17d** when compound **16d** was treated with NaOMe in methanol. The disappearance of the double bond indicates that the 1,4-addition of the methyl acrylate **16d** may occur under this condition. In order to solve this problem, we tried to use different coupling reagent to achieve the lactonization. Under the catalysis of ATPB, the secondary alcohol **13d** was protected as OTHP **18d** in excellent yield. The ozonolysis of alkene **18d** followed by our standard α-methylenation protocol afforded the desired α-methylene aldehyde **19d**, which was subsequently treated with $NaClO_2$ to give the corresponding acrylic acid **20d**. The lactonization of the hydroxy-acid **20d** was achieved by treatment with *o*-nitrophenylsulfonyl chloride in the presence of Na_2CO_3 to give the ε-cyclohexyl-α-methylene-ε-caprolactone (**17d**) in 86% yield (Scheme 3). Herein, *o*-nitrophenylsulfonyl chloride was demonstrated to be an excellent reagent to promote the 4- and 7-membered ring α-methylene lactones formation from their hydroxy-acid precursors. The hydrogen chloride in methanol is suitable to accomplish the 5- and 6-membered ring α-methylenelactones formation from their acetoxy-ester precursors.

2.3. Preparation of geminal di-substituted α-methylene lactones with different ring size

The tertiary alcohols **24a**-**24d**, prepared from the addition of alkenylmagnesium bromides to acetophenone (**22**) and cyclohexanone (**23**) respectively, were treated with acetic anhydride to give the acetates **25a**-**25d** in excellent yield (Scheme 4). The ozonolysis of alkene **25a** followed by our standard α-methylenation protocol gave the desired α-methylene aldehyde **26a**. The α-substituted acrolein **26a** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give methyl acrylate **27a** in excellent yield. The lactonization of the acetoxy-ester **27a** was achieved by treatment with a trace amount of HCl in methanol to give α-methylene-γ-butyrolactone **28a** in 75% yield. The α-methylene-γ-butyrolactone **28c** was also prepared in the similar manner from the corresponding alkene **24c**. The chemical yields in each step are good to excellent (Scheme 4). Mechanistically, the acetoxy group of compound **27a** will undergo methanolysis to give the corresponding hydroxy compound as an intermediate, which then undergoes 5-membered ring formation.

Since the 5-membered ring α-methylene lactones (**28a** and **28c**) were successfully formed under acidic condition, we tried to prepare their 6-membered ring analogues (**28b** and **28d**) from their acyclic precursors (**27b** and **27d**) under similar conditions. However, we obtained the elimination products rather than the ring formation products in each case. It is well known that 6-membered ring formation is slower than that of the 5-membered ring. Before the lactonization, the tertiary hydroxy compounds derived from **27b** and **27d** prefer to form the relatively stable tertiary carbocation intermediates, which may further undergo α-proton elimination. In order to solve this



Scheme 4. Reagents and conditions: (i) $CH_2{=}CH(CH_2)_nMgBr$, THF, −78 °C; (ii) Ac_2O, cat. DMAP, CH_2Cl_2; (iii) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv.=5:15); (iv) 2.3 mol equiv. $NaClO_2$, *t*-BuOH, 2 mol equiv. $NaH_2PO_4{-}2H_2O$, 3 mol equiv. $MeCH{=}CMe_2$; (v) CH_2N_2; (vi) cat. AcCl, MeOH; (vii) K_2CO_3, MeOH; (viii) *o*-NO_2PhSO_2Cl, Na_2CO_3, CH_2Cl_2.

problem, we considered to use *o*-nitrophenylsulfonyl chloride as the promoter. The acetoxy-acrolein **26b** was oxidized by sodium chlorite to give the acetoxy-acrylic acid **29b**, in which the acetoxy group was converted to give the hydroxy-acrylic acid **30b** in good yield. The lactonization of the hydoxy-acid **30b** was successfully achieved by treatment with *o*-nitrophenylsulfonyl chloride in the presence of Na_2CO_3 to give α-methylene-δ-valerolactone **28b** in 71% yield. The 6-membered ring α-methylenespirolactone **28d** was also prepared under similar condition from the hydroxy-acid **30d** (Scheme 4).

2.4. Preparation of bicyclic α-methylene lactones with different ring size

The cyclic *trans*-alcohols **32a**-**32b**, prepared from the addition of alkenylmagnesium bromides with 1,2-epoxy-cyclohexane (**31**) in the presence of CuI, were treated with acetic anhydride to give the acetates **33a**-**33b** in excellent yields (Scheme 5). The ozonolysis of alkene **33a** followed by our standard α-methylenation protocol gave the desired α-methylene aldehyde **34a**. The α-substituted acrolein **34a** was oxidized by sodium chlorite followed by treatment with CH_2N_2 to give the methyl acrylate **35a** in excellent yield. The lactonization of the acetoxy-ester **35a** was achieved by treatment with a catalytic amount of HCl in methanol to give the *trans*-fused bicyclic α-methylenelactone **36a** in 89% yield. The 6-membered ring analogues **36b** were also prepared in a similar manner from the corresponding terminal alkene precursor **33b**. The chemical yields in each step are good to excellent (Scheme 5).

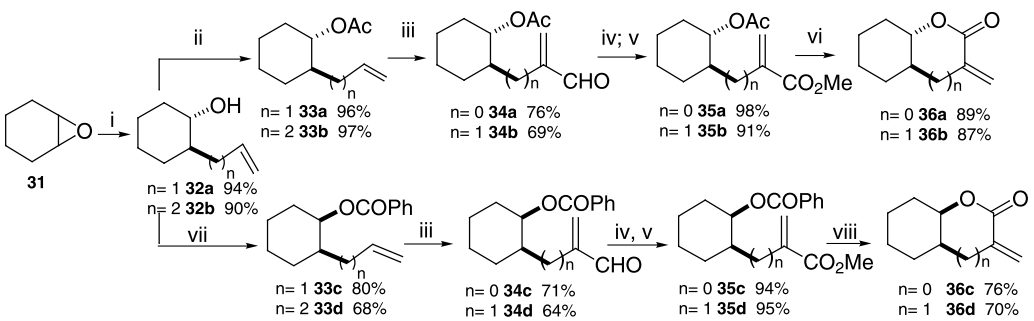
In order to prepare the *cis*-fused bicyclic lactones, the inversion of the hydroxy stereogenic centers of compounds **32a** and **32b** was achieved by Mitsunobu reaction[35] to give the corresponding *cis*-benzoxy-alkene **33c** and **33d** in good yields. Since the benzoate group of compound **35c** is more reluctant to methanolysis under acidic condition, we tried to use the basic condition to achieve the lactonization. When compound **35c** was treated with NaOMe in MeOH, we obtained the *cis*-fused bicyclic α-methylene-γ-lactone **36c** in 76% yield. The 6-membered ring *cis*-fused bicyclic analogue **36d** was also prepared in a similar manner (Scheme 5).

In order to demonstrate the applicability of our methodology to prepare the benzo-fused bicyclic α-methylene lactones with different ring size, 2-allylphenol (**37**) was used as the starting material. The phenolic group of compound **37** was protected as OTHP **38** in good yield. The ozonolysis of alkene **38** followed by our standard α-methylenation protocol in the same flask gave the desired α-methylene aldehyde **39**. The α-substituted acrolein **39** was oxidized by sodium chlorite, followed by treatment with CH_2N_2 to give methyl acrylate **40** in excellent yield. When compound **40** was treated with a catalytic amount of acetyl chloride in the presence of methanol, the reaction was quite messy and we did not obtain the desired lactone **42**. α-Methylene lactone **42** is known to be unstable and it is sensitive to the nucleophilic solvent.[36] Therefore, the OTHP group of compound **40** was deprotected to give the corresponding hydroxy-acrylate **41**. Compound **41** was treated with trifluoroacetic acid in toluene at 90 °C for 2 h[37] to give the desired product **42**. The crude product was confirmed by the ^1H NMR. Since it is too unstable to be purified by silica gel column chromatography, the crude product **42** was then treated with cyclopentadiene to give the Diels–Alder adduct **43** as a mixture of two diastereomers in a ratio of 4 to 1 in 51% overall yield from compound **41**. We found that the major adduct was a less polar isomer.

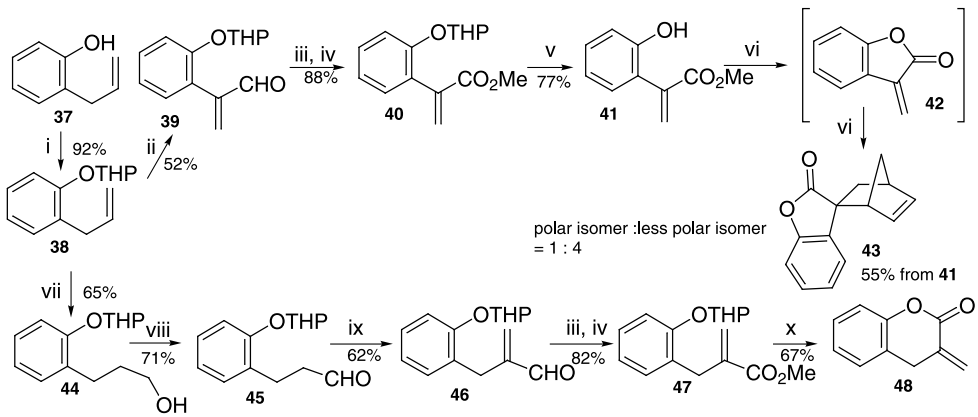
For the purpose to prepare the 6-membered ring benzo-fused bicyclic α-methylene lactone from compound **38**, elongation of the side chain is required. The hydroboration of the alkene **38** followed by treatment with hydrogen peroxide gave the corresponding primary alcohol **44** in 65% yield. The alcohol **44** was oxidized by PCC to give the corresponding aldehyde **45**. By using our standard α-methylenation protocol, the aldehyde **45** was converted to the desired α-methylene aldehyde **46** in 62% yield. The α-substituted acrolein **46** was oxidized by sodium chlorite followed by treatment with CH_2N_2 to give methyl acrylate **47** in excellent yield. The OTHP-acrylate **47** was treated with a catalytic amount of acetyl chloride in the presence of methanol to give benzo-fused α-methylene-γ-valerolactone **48** in good yield (Scheme 6). No double bond isomerization occurred during this acid-catalyzed lactonization.

2.5. Preparation of mono-substituted α-methylene lactams with different ring size

In order to demonstrate the applicability of our methodology to prepare the α-methylene lactams with different ring size, the secondary alcohol **12c** and **12d** were converted to the corresponding azides **49c** and **49d** by Mitsunobu reaction condition[38] in good yields. We found that these azides were



Scheme 5. Reagents and conditions: (i) cat. CuI, $CH_2{=}CH(CH_2)nMgBr$, THF, −78 °C; (ii) cat. DMAP, pyridine, Ac_2O, CH_2Cl_2; (iii) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv.=5:15); (iv) 2.3 mol equiv. $NaClO_2$, *t*-BuOH, 2 mol equiv. $NaH_2PO_4{\cdot}2H_2O$, 3 mol equiv. $MeCH{=}CMe_2$; (v) CH_2N_2; (vi) cat. AcCl, MeOH; (vii) $PhCO_2H$, DEAD, Ph_3P; (viii) NaOMe, MeOH.



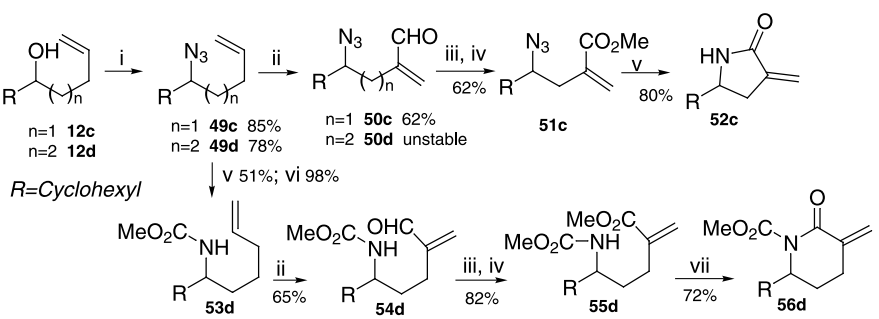
Scheme 6. Reagents and conditions: (i) cat. ATPB, dihydropyran; (ii) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv.=5:15); (iii) 2.3 mol equiv. $NaClO_2$, *t*-BuOH, 2 mol equiv. $NaH_2PO_4{-}2H_2O$, 3 mol equiv. $MeCH{=}CMe_2$; (iv) CH_2N_2; (v) cat. ATPB, MeOH; (vi) (a) CF_3CO_2H, toluene, 90 °C; (b) cyclopentadiene; (vii) (a) 9-BBN; (b) H_2O_2, NaOH; ; (viii) PCC, CH_2Cl_2. (ix) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv.=4:15); (x) cat. AcCl, MeOH.

decomposed slowly by the silica gel. However, they can still be purified by flash silica gel column chromatograpy. It is worthy to mention that both of these compounds are photosensitive and decomposed rapidly at room temperature in the pure state. Therefore, they must be freshly prepared and used directly for further reaction. The ozonolysis of azido-alkene **49c** followed by our standard α-methylenation protocol gave the desired α-methylene aldehyde **50c**. The azido group is compatible with the ozone treatment. The freshly prepared azido-acrolein **50c** was oxidized by sodium chlorite to give the corresponding acrylic acid, which was subsequently treated with CH_2N_2 to give azido-acrylate **51c** in good yield. Compound **51c** was treated with triphenylphosphine followed by the addition of water to give the α-methylene-γ-butyrolactam **52c** in 80% yield (Scheme 7).

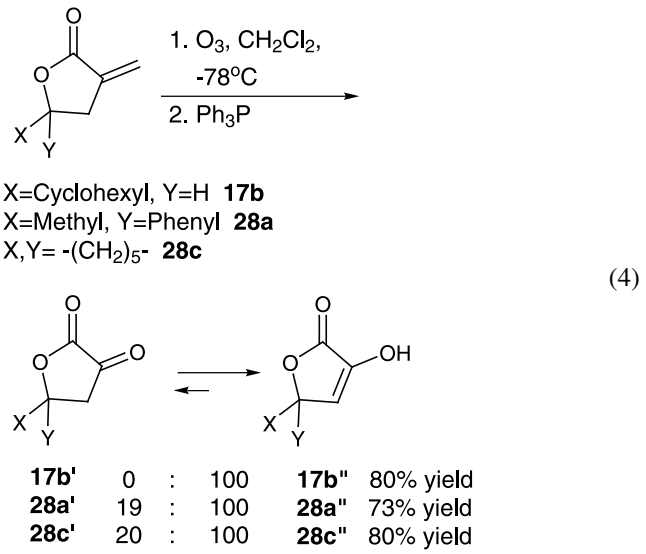
Although the azido compounds **49c**, **50c** and **51c** are not quite stable, they are still applicable to further functional group transformations. To our surprise, the azido-acrolein **50d** is more unstable than **50c**. It was decomposed quickly by silica gel during the separation and too unstable to the further transformations. In order to solve this problem, the azido group of compound **49d** was reduced with Ph_3P followed by treatment with water to give the corresponding amino compound, which was then treated with methyl chloroformate to give carbamate **53d** in high yield. The ozonolysis of carbamato-alkene **53d** followed by our standard α-methylenation protocol in the same flask gave the desired α-methylene aldehyde **54d**. According to the above-mentioned reaction sequences, the carbamato-acrolein **55d** was converted to the carbamato-acrylate **55d** in excellent yield. The lactamization of compound **55d** was achieved by the treatment of trimethylaluminium in toluene to give α-methylene-δ-valerolactam **56d** in 72% yield (Scheme 7).[39]

2.6. Preparation of α-keto lactones with different ring size from the corresponding α-methylene lactones

We have been successful employing our methodology to prepare 4- to 7-membered ring α-methylenelactones. We tried to cleave their α-methylene groups by ozone in order to prepare the corresponding α-keto lactones. The ozonolysis of 5-membered ring α-methylene-γ-lactone **17b** in CH_2Cl_2 at −78 °C followed by the reduction with Ph_3P gave the corresponding α-keto-γ-butyrolactone **17b′** as an intermediate which tautomerized completely to its enol form **17b″**. In $CDCl_3$, no keto form isomer **17b′** was detected by ^1H and ^{13}C NMR spectroscopy. The characteristic peaks of the ^{13}C NMR spectrum for compound **17b″** are the ones at δ 170.3 ppm for the carbonyl carbon, δ 142.2 ppm for the α-carbon, and δ 117.6 ppm for the β-carbon. No absorption appears above δ 170.3 ppm in the ^{13}C NMR spectrum as well as none appears between δ 2–4 ppm in the ^1H NMR spectrum indicate that there is no keto isomer present in the solution (Eq. 4).



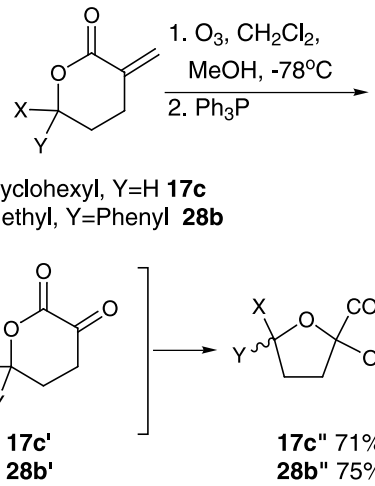
Scheme 7. Reagents and conditions: (i) DEAD, Ph_3P, $(PhO)_2PON_3$; (ii) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2 (mol equiv.=5:15); (iii) 2.3 mol equiv. $NaClO_2$, *t*-BuOH, 2mol equiv. $NaH_2PO_4{-}2H_2O$, 3 mol equiv. $MeCH{=}CMe_2$; (iv) CH_2N_2; (v) Ph_3P; H_2O; (vi) $ClCO_2Me$, K_2CO_3; (vii) Me_3Al, toluene.



(4)

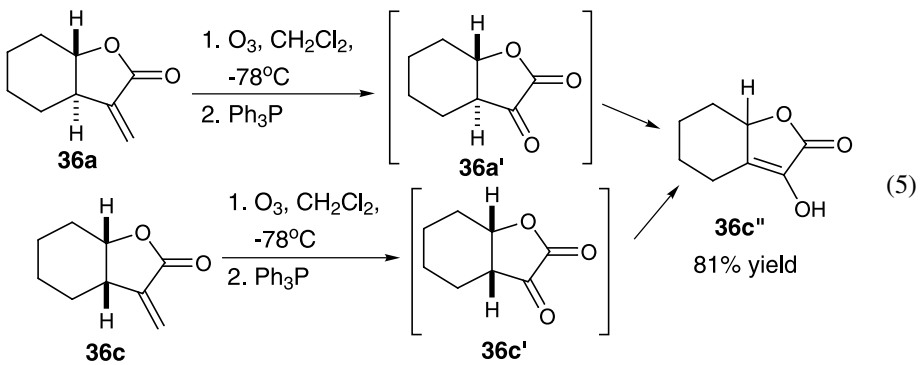
The ozonolysis of the γ,γ-disubstituted-α-methylene-γ-lactone **28a** followed by reduction with Ph_3P gave the α-keto-γ-butyrolactone **28a′** as an intermediate which equilibrated with its enol form **28a″**. The β-olefinic proton absorption of compound **28a″** appears at δ 6.52 ppm as a singlet in $CDCl_3$. The methylene group adjacent to the keto group of compound **28a′** appears as AB-type splitting pattern at δ 3.18–3.20 ppm. The ratio of the enol form (**28a″**) and keto form (**28a′**) is 100:19 as estimated by integrations (Eq. 4). Under similar reaction condition, the γ,γ-disubstituted-α-methylenespirolactone **28c** was converted to the α-keto-γ-butyrolactone **28c′** as an intermediate which equilibrated with its enol form **28c″**. The β-olefinic proton absorption of compound **28c″** appears at δ 6.31 ppm as a singlet in $CDCl_3$. The methylene group adjacent to the keto group of compound **28c′** appears as a singlet at δ 2.75 ppm. The isomeric ratio of the enol form (**28c″**) and keto form (**28c′**) is 100:20 as estimated by integrations (Eq. 4).

the carbonyl carbon, δ 135.0 ppm for the α-carbon and δ 134.0 ppm for the β-carbon. No absorption appears above δ 170.9 ppm in ^{13}C NMR spectrum indicates that there is no keto isomer present in the solution (Eq. 5).



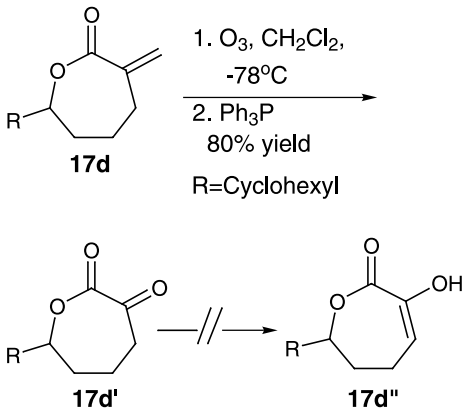
(6)

According to the above-mentioned ozonolysis condition, the 6-membered ring α-methylene lactones (**17c** and **28b**) gave complicated mixtures. The ozonolysis of the α-methylene-δ-valerolactones (**17c** and **28b**) in dichloromethane at −78 °C followed by treatment with Et_3N[40] also gave a complicated mixture. Interestingly, when compound **17c** was treated with ozone in the presence of methanol, we isolated the 5-membered ring lactol (**17c″**) as a mixture of two diastereomers, which were derived from the skeletal rearrangement of the corresponding α-keto-δ-caprolactones (**17c′**) intermediate. The characteristic peaks of the ^{13}C NMR spectrum for compound **17c″** are the absorptions at δ 171.8 ppm for the carbonyl carbon and δ 102.0 and 101.5 ppm for quarternary carbon bearing the hydroxy group. No absorption appears above δ 171.8 ppm in ^{13}C NMR spectrum indicates that there is no keto group present



(5)

The ozonolysis of both the *cis*- and *trans*-bicyclic α-methylene-γ-lactones (**36a** and **36c**) followed by reduction with Ph_3P gave the enol product **36c″** only (Eq. 5). The characteristic peaks of the ^{13}C NMR spectrum for compound **36c″** are the absorptions at δ 170.9 ppm for in product **17c″** (Eq. 7). A broad and strong OH absorption at 3447 cm^{-1} in the infrared spectrum also supports the structure of compound **17c″**. Similar result was obtained from the ozonolysis of compound **28b** in the presence of methanol (Eq. 6).



(7)

The ozonolysis of 7-membered ring α-methylene lactone **17d** in CH_2Cl_2 at −78 °C followed by the reduction with Ph_3P gave the corresponding α-keto-γ-lactone **17d′**, which does not equilibrate to its enol form **17d″** in $CDCl_3$ as judged from its ^{13}C NMR spectrum (Eq. 7). The characteristic peaks of the ^{13}C NMR spectrum for compound **17d′** are the absorptions at δ 200.1 ppm for the keto carbonyl carbon and at δ 166.2 ppm for the lactone carbonyl carbon. No absorption appeares between 100–160 ppm in ^{13}C NMR spectrum indicates that there is no enol isomer present in the solution (Eq. 7).

3. Conclusions

In summary, we have developed a general methodology to prepare the acyclic α-substituted acrylic acids and their derivatives from the corresponding terminal alkenes. The further cleavage of their α-methylene groups by the ozonolysis gave the corresponding α-keto acid derivatives in good yields. The reaction conditions in each step are quite mild that substrates with labile functional groups can be used. This methodology can also be applied to prepare 4- to 7-membered ring α-methylene lactones in good yields. For the 5- and 7-membered ring α-methylenelactones, the further cleavage of their α-methylene groups by the ozonolysis in CH_2Cl_2 gave the corresponding α-keto lactones in good yields. Their tautomeric ratio is ring-size and substituent-dependent. For the 6-membered ring α-methylene lactones, the further cleavage of their α-methylene groups by the ozonolysis in the presence of methanol gave the skeletal rearranged 5-membered ring lactols in good yields.

4. Experimental

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Bruker ACP 300 and Bruker Avance DPX400 spectrometer, and chemical shifts were given in ppm downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorptions were listed. Mass spectra were measured on a Micromass Trio-2000 GC/MS spectrometer (National Chiao–Tung University) by electronic impact at 70 eV (unless otherwise indicated). High Resolution Mass Spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT (National Chung Hsing University) or VG-11-250J (Academia Sinica) Mass Spectrometer. α-Substituted acroleins **4a**-**4f** were prepared from terminal alkenes **1a**-**1f** according to our report.[1b]

4.1. General procedure to prepare the secondary alcohol from Grignard reagent with carbonyl compound

Allyl bromide (1/10 of 5.81 g, 48 mmol) is added, without stirring, to a mixture of magnesium turings (1.21 g, 50 mmol) in 10 mL of anhydrous THF. After the reaction started, the remaining allyl bromide in 10 mL of THF is added dropwise with stirring so that the THF barely refluxes. The mixture is then refluxed for 2 h, cooled to room temperature, and added 20 mL of THF to dilute the Grignard reagent. To a solution of cyclohexanecarbaldehyde (**12**) (4.71 g, 42 mmol) in 40 mL of THF was added the Grignard reagent dropwise at −78 °C and stirred at this temperature for 1 h. The reaction is quenched with aqueous ammonium chloride solution and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, concentrated, and chromatographed on silica gel column to give the secondary alcohol **13a** (5.95 g, 38.6 mmol) in 92% yield.

4.1.1. 1-Cyclohexylbut-3-en-1-ol (13a).[41] 92% Yield; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.79–5.87 (m, 1H, $-CH{=}CH_2$), 5.11–5.16 (m, 2H, $-CH{=}CH_2$), 3.37–3.41 (m, 1H, $CH-OH$), 2.30–2.40 (m, 1H, $-CH_2-CH{=}CH_2$), 2.05–2.15 (m, 1H, $-CH_2-CH{=}CH_2$), 1.01–1.77 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 117.7, 74.7, 43.0, 38.8, 29.1, 28.0, 26.5, 26.2, 26.1; IR (CH_2Cl_2, cm^{-1}): 3390 (OH), 3074, 2976, 2924, 2852, 1639, 1449, 985, 911; MS *m/z* (rel intensity): 144 (M^+-18, 4), 113 (M^+-41, 2), 95 (100), 67 (18); HRMS Calcd for $C_{10}H_{18}O-CH_2-CH{=}CH_2$ 113.0967, found:113.0961.

4.1.2. 1-Cyclohexylpent-4-en-1-ol (13b).[42] 82% Yield, TLC R_f=0.32 (hexane/EtOAc=10:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.80–5.87 (m, 1H, $-CH{=}CH_2$), 4.94–5.06 (m, 2H, $-CH{=}CH_2$), 3.34–3.38 (m, 1H, $CH-OH$), 2.25–2.32 (m, 1H, $-CH_2-CH{=}CH_2$), 2.11–2.18 (m, 1H, $-CH_2-CH{=}CH_2$), 1.01–1.77 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 114.6, 75.7, 43.7, 33.3, 30.3, 29.2, 27.8, 26.5, 26.3, 26.2; IR (CH_2Cl_2, cm^{-1}): 3398 (OH), 3077, 1450, 1085, 985, 910; MS *m/z* (rel intensity): 168 (M^+, 2), 111 (52), 109 (32), 83 (100), 55 (82); HRMS Calcd for $C_{11}H_{20}O$ 168.1514, found: 168.1516.

4.1.3. 1-Cyclohexylhex-5-en-1-ol (13c).[42] 85% Yield, TLC R_f=0.34 (hexane/EtOAc=10:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.83 (m, 1H, $-CH{=}CH_2$), 4.91–5.01 (m, 2H, $-CH{=}CH_2$), 3.32–3.34 (m, 1H, $CH-O$), 2.05–2.07 (m, 2H, $-CH_2-CH{=}CH_2$), 1.06–1.76 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 114.5, 76.0, 43.6, 33.7, 33.5, 29.2, 27.7, 26.5, 26.3, 26.2, 25.2; IR (CH_2Cl_2, cm^{-1}): 3323 (OH), 3076, 2978, 2924, 1450, 1086, 909; MS *m/z* (rel intensity): 182 (M^+, 7), 95 (33), 81 (36), 55 (39), 41 (52); HRMS Calcd for $C_{12}H_{22}O$ 182.1671, found: 182.1665.

4.1.4. 1-Cyclohexylhept-6-en-1-ol (13d). 80% Yield, TLC R_f=0.35 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.82 (m, 1H, –C*H*=CH_2), 4.89–5.00 (m, 2H, –CH=CH_2), 3.31 (br, 1H, C*H*–OH), 2.03–2.05 (m, 2H, –CH_2–CH=CH_2), 0.86–1.76 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 114.2, 76.0, 43.5, 33.9, 33.7, 29.2, 29.0, 27.7, 26.5, 26.3, 26.2, 25.4; IR (CH_2Cl_2, cm^{-1}): 3420 (OH), 3076, 2926, 1451, 1086; MS *m*/*z* (rel intensity): 196 (M^+, 2), 113 (23), 95 (100), 69 (16), 55 (13); HRMS Calcd for $C_{13}H_{24}O$ 196.1827, found: 196.1835.

4.1.5. 2-Phenylhex-5-en-2-ol (24a).[43] 90% Yield, TLC R_f=0.35 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.46 (m, 5H), 5.76–5.85 (m, 1H, –C*H*=CH_2), 4.93–5.01 (m, 2H, –CH=CH_2), 1.89–2.11 (m, 4H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.6, 138.7, 128.1, 126.5, 124.7, 114.5, 74.6, 43.0, 30.2, 28.4; IR (CH_2Cl_2, cm^{-1}): 3420 (OH), 3025, 2926, 1638, 1456, 997, 912; MS *m*/*z* (rel intensity): 176 (M^+, 7), 121 (100), 105 (22), 77 (12), 43 (43); HRMS Calcd for $C_{12}H_{16}O$ 176.1201, found: 176.1200.

4.1.6. 2-Phenylhept-6-en-2-ol (24b).[44] 81% Yield, TLC R_f=0.38 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41–7.43 (m, 2H), 7.30–7.34 (m, 2H), 7.20–7.24 (m, 1H), 5.69–5.76 (m, 1H, –C*H*=CH_2), 4.89–4.97 (m, 2H, –CH=CH_2), 1.96–2.02 (m, 2H, –CH_2–CH=CH_2), 1.77–1.82 (m, 2H), 1.54 (s, 3H), 1.35–1.38 (m, 1H), 1.23–1.35 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.9, 138.6, 128.1, 126.5, 124.7, 114.6, 74.6, 43.6, 33.9, 30.1, 23.2; IR (CH_2Cl_2, cm^{-1}): 3407 (OH), 3063, 2929, 1753, 1678, 1493, 997, 911; MS *m*/*z* (rel intensity): 190 (M^+, 3), 175 (8), 121 (100), 105 (13), 43 (37); HRMS Calcd for $C_{13}H_{18}O$ 190.1358, found: 190.1351.

4.1.7. 1-But-3-enylcyclohexanol (24c).[45] 86% Yield, TLC R_f=0.4 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80–5.90 (m, 1H, –C*H*=CH_2), 4.93–5.05 (m, 2H, CH=CH_2), 2.13–2.15 (m, 2H, CH_2–CH=CH_2), 1.27–1.70 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.3, 114.2, 71.3, 41.4, 37.4, 27.4, 25.8, 22.2; IR (CH_2Cl_2, cm^{-1}): 3375 (OH), 3077, 2923, 2852, 1640, 1450, 985, 912; MS *m*/*z* (rel intensity): 136 (M^+–18), 99 (65), 98 (100), 81 (50), 55 (63); HRMS Calcd for $C_{10}H_{18}O$–H_2O 136.1252, found: 136.1249.

4.1.8. 1-Pent-4-enylcyclohexanol (24d).[45] 80% Yield, TLC R_f=0.42 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78–5.85 (m, 1H, –C*H*=CH_2), 4.93–5.03 (m, 2H, CH=CH_2), 2.05–2.06 (m, 2H, CH_2–CH=CH_2), 1.43–1.58 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.8, 114.4, 71.3, 41.8, 37.3, 34.2, 25.8, 22.2, 22.1; IR (CH_2Cl_2, cm^{-1}): 3330 (OH), 3077, 2928, 2856, 1640, 1449, 997, 910; MS *m*/*z* (rel intensity): 150 (M^+–18, 33), 99 (62), 98 (100), 81 (41), 55 (36); HRMS Calcd for $C_{11}H_{20}O$–H_2O 150.1409, found: 150.1402.

4.2. General procedure to prepare the secondary alcohol from Grignard reagent with epoxide

Allylmagnesium bromide obtained from allyl bromide (847 mg, 7.0 mmol) and magnesium powder (243 mg, 10.0 mmol) in THF. The Grignard reagent was added to a well-stirred suspension of copper(I) iodide (171 mg, 0.9 mmol) in 10 mL of THF at −5 °C. After the copper iodide dissolved (*ca*. 30 min) the solution is cooled to −20 °C, and cyclohexene oxide (588 mg, 6 mmol) is added dropwise. The reaction is warmed slowly to room temperature and stirred at room temperature for 10 h. The reaction mixture is poured into 10 mL of iced cold, saturated NH_4Cl solution. The aqueous phase is extracted with saturated NaCl solution, dried over $MgSO_4$, concentrated and chromatographed on silica gel column to give the alcohol **32a** as colorless oil (789 mg, 5.64 mmol) in 94% yield.

4.2.1. *trans*-2-Allylcyclohexanol (32a).[46] 94% Yield, TLC R_f=0.30 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.78–5.84 (m, 1H, –C*H*=CH_2), 4.96–5.04 (m, 2H, –CH=CH_2), 3.19–3.23 (m, 1H, C*H*–OH), 2.41–2.44 (m, 1H, –CH_2–CH=CH_2), 2.05–2.08 (m, 1H, –CH_2–CH=CH_2), 0.91–1.94 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.4, 115.8, 74.4, 44.8, 37.2, 35.5, 30.2, 25.4, 24.8; IR (CH_2Cl_2, cm^{-1}): 3445 (OH), 3025, 2925, 1637, 1495, 1027; MS *m*/*z* (rel intensity): 122 (M^+−18, 62), 98 (59), 93 (56), 81 (100), 79 (58); HRMS Calcd for $C_9H_{16}O$–H_2O 122.1096, found: 122.1086.

4.2.2. *trans*-2-But-3-enylcyclohexanol (32b). 90% Yield, TLC R_f=0.33 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.79–5.86 (m, 1H, –C*H*=CH_2), 4.92–5.04 (m, 2H, –CH=CH_2), 3.36–3.41 (m, 1H, C*H*–OH), 2.18–2.22 (m, 1H, –CH_2–CH=CH_2), 2.11–2.15 (m, 1H, –CH_2–CH=CH_2), 1.18–1.85 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 114.5, 75.3, 46.3, 35.2, 30.1, 29.1, 28.5, 25.6, 25.5; IR (CH_2Cl_2, cm^{-1}): 3398 (OH), 3014, 1455, 1055; MS *m*/*z* (rel intensity): 136 (M^+−18, 30), 97 (M^+−57, 30), 81 (100), 67 (48), 43 (40), 41 (63); HRMS Calcd for $C_{10}H_{18}O$ 154.1358, found: 154.1361.

4.3. General procedure to prepare the acetate from the corresponding alcohol

To a solution of secondary alcohol **13a** (1.0 g, 6.5 mmol), pyridine (0.63 mL, 7.8 mmol) and a catalytic amount of DMAP (*N*,*N*-dimethylaminopyridine, 9.52 mg, 0.78 mmol) in 25 mL of CH_2Cl_2 was added acetic anhydride (0.74 mL, 7.8 mmol). The reaction mixture was stirred at room temperature for 10 h. The reaction mixture was concentrated, chromatographed on silica gel column to give the corresponding acetate **14a** (1.27 g, 6.5 mmol) in 95% yield.

4.3.1. 1-Cyclohexylbut-3-enyl acetate (14a).[47] 95% Yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71–5.77 (m, 1H, –C*H*=CH_2), 5.02–5.08 (m, 2H, –CH=CH_2), 4.76–4.80 (m, 1H, C*H*–OAc), 2.20–2.40 (m, 2H, –CH_2–CH=CH_2), 2.03 (s, 3H, –COCH_3), 0.99–1.75 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 134.2, 117.2, 76.7, 40.7, 35.9, 29.0, 28.1, 26.3, 26.0, 25.9, 21.0; IR (CH_2Cl_2, cm^{-1}): 3077, 2928, 2854, 1738, 1644, 1540, 1449, 1371, 914, 834; MS *m*/*z* (rel intensity): 155 (M^+−41, 15), 136 (M^+−60, 8), 95 (100), 83 (34), 69 (26), 55 (40); HRMS Calcd for $C_{12}H_{20}O_2$–CH_2CH=CH_2 155.1072, found:. 155.1070.

4.3.2. 1-Cyclohexylpent-4-enyl acetate (14b). 93% Yield, TLC R_f=0.7 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$,

400 MHz) δ 5.75–5.82 (m, 1H, –C*H*=CH_2), 4.93–5.01 (m, 2H, –CH=CH_2), 4.73–4.78 (m, 1H, C*H*–OAc), 2.00–2.04 (m, 2H, –CH_2–CH=CH_2), 2.01 (s, 3H, –COCH_3), 0.98–1.74 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 138.1, 114.7, 77.4, 41.3, 30.5, 29.8, 28.9, 28.1, 26.4, 26.1, 26.0, 21.1; IR (CH_2Cl_2, cm^{-1}): 3077, 2927, 2854, 1737, 1449, 1371, 940, 912; MS *m*/*z* (rel intensity): 210 (M^+, 3), 95 (12), 43 (100), 41 (24), 32 (42); HRMS Calcd for $C_{13}H_{22}O_2$ 210.1620, found: 210.1621.

4.3.3. 1-Cyclohexylhex-5-enyl acetate (14c). 90% Yield, TLC R_f=0.7 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.70–5.76 (m, 1H, –C*H*=CH_2), 4.89–4.97 (m, 2H, –CH=CH_2), 4.70–4.71 (m, 1H, C*H*–OAc), 1.98–2.02 (m, 2H, –CH_2–CH=CH_2), 2.00 (s, 3H, –COCH_3), 0.97–1.67 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 138.3, 114.6, 77.6, 41.2, 33.5, 30.5, 28.9, 28.0, 26.3, 26.04, 26.00, 24.6, 20.9; IR (CH_2Cl_2, cm^{-1}): 3075, 2928, 2854, 1736, 1449, 1371, 965, 909; MS *m*/*z* (rel intensity): 181 (M^+−43, 3), 95 (18), 81 (21), 43 (100), 32 (51); HRMS Calcd for $C_{14}H_{24}O_2$ 224.1776, found: 224.1767.

4.3.4. 1-Cyclohexylhept-6-enyl acetate (14d). 91% Yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76–5.82 (m, 1H, –C*H*=CH_2), 4.92–5.01 (m, 2H, –CH=CH_2), 4.72–4.75 (m, 1H, C*H*–OAc), 2.03–2.05 (m, 2H, –CH_2–CH=CH_2), 2.04 (s, 3H, –COCH_3), 0.98–1.67 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 138.8, 114.3, 77.9, 41.2, 33.6, 31.0, 29.0, 28.8, 28.1, 26.4, 26.12, 26.05, 24.9, 21.1; IR (CH_2Cl_2, cm^{-1}): 3076, 2928, 2854, 1735, 1639, 1540, 1450, 1370, 1242, 1019, 993, 970; MS *m*/*z* (rel intensity): 238 (M^+, 4), 167 (M^+−60, 8), 149 (24), 111 (54), 95 (68), 83 (100), 71 (48), 69 (51), 57 (76), 55 (98); HRMS Calcd for $C_{15}H_{26}O_2$ 238.1933, found:.238.1937.

4.3.5. 2-Phenylhex-5-enyl acetate (25a). 93% Yield, TLC R_f=0.50 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22–7.35 (m, 5H), 5.70–5.79 (m, 1H, –C*H*=CH_2), 4.91–5.00 (m, 2H, –CH=CH_2), 1.94–2.16 (m, 4H), 2.05 (s, 3H, –COCH_3), 1.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 144.7, 138.0, 128.1, 127.0, 124.4, 114.5, 83.7, 41.5, 28.1, 24.9, 22.1; IR (CH_2Cl_2, cm^{-1}): 3024, 2934, 1736, 1639, 1496, 1367, 1014, 734; MS *m*/*z* (rel intensity): 158 (M^+−60, 18), 143 (19), 121 (100), 105 (21), 43 (20); HRMS Calcd for $C_{14}H_{18}O_2$ 218.1307, found: 218.1311.

4.3.6. 2-Phenylhept-6-enyl acetate (25b). 91% Yield, TLC R_f=0.51 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20–7.33 (m, 5H), 5.68–5.75 (m, 1H, –C*H*=CH_2), 4.90–4.98 (m, 2H, –CH=CH_2), 1.95–2.05 (m, 4H), 2.04 (s, 3H, –COCH_3), 1.82 (s, 3H), 1.27–1.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 144.9, 138.3, 128.1, 126.7, 124.4, 114.6, 83.9, 41.9, 33.6, 24.8, 22.9, 22.1; IR (CH_2Cl_2, cm^{-1}): 3027, 2937, 1734, 1640, 1496, 1364, 1016, 735; MS *m*/*z* (rel intensity): 232 (M^+, 2), 163 (23), 131 (13), 121 (100), 43 (27); HRMS Calcd for $C_{15}H_{20}O_2$ 232.1463, found: 232.1470.

4.3.7. 1-But-3-enylcyclohexyl acetate (25c).[48] 94% Yield, TLC R_f=0.60 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75–5.82 (m, 1H, –C*H*=CH_2), 4.91–5.02 (m, 2H, –CH=CH_2), 2.17–2.21 (m, 2H, CH_2–CH=CH_2), 2.02 (s, 3H, –COCH_3), 1.94–2.01 (m, 2H), 1.24–1.51 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 138.6, 114.3, 83.6, 36.6, 34.5, 27.5, 25.5, 22.2, 21.8; IR (CH_2Cl_2, cm^{-1}): 3077, 2933, 2860, 1731, 1450, 1367, 963, 910; MS *m*/*z* (rel intensity): 141 (M^+−55, 10), 136 (M^+−60, 60), 98 (80), 80 (62), 55 (91), 43 (100); HRMS Calcd for $C_{12}H_{20}O_2$ 196.1463, found: 196.1472.

4.3.8. 1-Pent-4-enylcyclohexyl acetate (25d). 92% Yield, TLC R_f=0.60 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.69–5.77 (m, 1H, –C*H*=CH_2), 4.88–4.96 (m, 2H, –CH=CH_2), 2.11–2.14 (m, 2H, –CH_2–CH=CH_2), 1.95 (s, 3H, –COCH_3), 1.96–1.99 (m, 2H), 1.80–1.84 (m, 2H), 1.18–1.47 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ170.2, 138.5, 114.4, 83.7, 36.9, 34.4, 33.8, 25.5, 22.3, 22.0, 21.7; IR (CH_2Cl_2, cm^{-1}): 3077, 2932, 2861, 1732, 1449, 1366, 966, 910; MS *m*/*z* (rel intensity): 150 (M^+−60, 18), 109 (40), 99 (100), 81 (48), 67 (43); HRMS Calcd for $C_{13}H_{22}O_2$ 210.1620, found: 210.1622.

4.3.9. *trans*-2-Allylcyclohexyl acetate (33a). 96% Yield, TLC R_f=0.7 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66–5.70 (m, 1H, –C*H*=CH_2), 4.90–4.95 (m, 2H, –CH=CH_2), 4.44–4.48 (m, 1H, C*H*OAc), 2.17–2.20 (m, 2H), 0.98–1.98 (m, 9H), 1.97 (s, 3H, –COCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 136.3, 115.9, 76.3, 41.6, 36.8, 31.7, 30.1, 25.0, 24.4, 21.1; IR (CH_2Cl_2, cm^{-1}): 3014, 2953, 2868, 1736, 1371, 944, 913; MS *m*/*z* (rel intensity): 140 (M^+−42, 20), 122 (100), 107 (33), 93 (52).

4.3.10. *trans*-2-But-3-enylcyclohexyl acetate (33b). 97% Yield, TLC R_f=0.7 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74–5.97 (m, 1H, –C*H*=CH_2), 4.92–5.00 (m, 2H, –CH=CH_2), 4.81–4.86 (m, 1H, C*H*OAc), 2.02–2.05 (m, 3H), 1.28–1.65 (m, 10H), 2.03 (s, 3H, –COCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 138.0, 114.7, 76.7, 43.8, 32.7, 29.7, 28.9, 28.5, 25.4, 25.2, 21.1; IR (CH_2Cl_2, cm^{-1}): 3071, 2950, 1738, 1450, 1373, 944, 912; MS *m*/*z* (rel intensity): 154 (M^+−42, 2), 95 (31), 81 (23), 43 (100), 41 (28).

4.4. General procedure to prepare the benzoate from the corresponding alcohol by Mitsunobu reaction

To a stirred suspension of Ph_3P (2.24 g, 8.57 mmol) and benzoic acid (1.05 g, 8.57 mmol) in toluene (25 mL) cooled to −30 °C was added a solution of secondary alcohol **32a** (1000 mg, 7.14 mmol) in toluene (5 mL). A solution of DEAD (diethyl azodicarboxylate, 1.492 g, 8.57 mmol) in toluene (10 mL) was added dropwise over 15 min to the vigorously stirred mixture while the temperature was maintained at −30 °C. When the addition was complete the mixture was allowed to warm gradually to 0 °C over 1 h where upon saturated aqueous sodium bicarbonate 30 (mL) was added. The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give the benzoate **33c** (1.39 g, 5.71 mmol) in 80% yield.

4.4.1. *cis*-2-Allylcyclohexyl benzoate (33c).[49] 80% Yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07–8.09 (m, 2H), 7.41–7.55 (m, 3H), 5.73–5.80 (m, 1H, –C*H*=CH_2), 5.27 (br s,

1H, C*H*OCOPh), 4.92–4.98 (m, 2H, –CH=CH_2), 1.26–2.15 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 136.5, 132.6, 130.9, 129.4, 128.2, 116.1, 72.4, 40.4, 36.9, 30.1, 27.4, 25.1, 20.9; IR (CH_2Cl_2, cm^{-1}): 3031, 2930, 2857, 1715, 1490, 1358, 1069; MS *m/z* (rel intensity): 244 (M^+, 3), 202 (8), 122 (53), 105 (100), 77 (27); HRMS Calcd for $C_{16}H_{20}O_2$ 244.1463, found: 244.1469.

4.4.2. *cis*-2-But-3-enylcyclohexyl benzoate (33d). 68% Yield, TLC R_f=0.78 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05–8.07 (m, 2H), 7.42–7.57 (m, 3H), 5.79–5.85 (m, 1H, –C*H*=CH$_2$), 5.13–5.18 (m, 1H, C*H*OCOPh), 4.94–5.04 (m, 2H, –CH=CH_2), 2.13–2.15 (m, 2H), 1.27–1.28 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.3, 138.0, 132.6, 130.7, 129.5, 128.3, 114.8, 77.5, 43.9, 32.9, 29.7, 29.0, 28.5, 25.5, 25.3; IR (CH_2Cl_2, cm^{-1}): 3032, 2949, 2867, 1715, 1451, 1069; MS *m/z* (rel intensity): 258 (M^+, 1), 121 (41), 105 (100), 77 (62), 67 (28); HRMS Calcd for $C_{17}H_{22}O_2$ 258.1620, found: 258.1629.

4.5. General procedure to prepare the tetrahydropyranyl ether from the corresponding alcohol

To a solution of alcohol **13a** (1.00 g, 6.5 mmol) and 3,4-dihydro-2*H*-pyran (0.65 mL, 7.2 mmol) in 20 mL of dichloromethane was added ATPB (0.26 g, 0.65 mmol) and the solution was stirred at room temperature. The reaction was complete in 30 min. The solution was concentrated and chromatographed on silica gel column to give the desired **18a** (1.47 g, 6.17 mmol) in 95% yield as a mixture of two diastereomers.

4.5.1. 2-(1-Cyclohexylbut-3-enyloxy)tetrahydropyran (18a). 95% Yield, a mixture of two diastereomers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74–5.88 (m, 1H, –C*H*=CH$_2$), 4.97–5.04 (m, 2H, –CH=CH_2), 4.66 and 4.64 (br, 1H, O–C*H*–O), 3.80–3.97 (m, 1H, C*H*–OTHP), 3.41–3.45 (m, 2H, CH_2–O–CH), 2.31–2.33 (m, 2H, –CH_2–CH=CH$_2$), 1.01–1.69 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.8, 135.1, 116.4, 115.9, 99.4, 96.8, 81.9, 79.3, 62.5, 62.4, 41.3, 40.6, 36.7, 34.6, 30.92, 30.91, 29.0, 28.8, 28.7, 26.6, 26.3, 26.27, 26.25, 26.22, 25.5, 19.8; IR (CH_2Cl_2, cm^{-1}): 3076, 2926, 2861, 1439, 1132, 1024; MS *m/z* (rel intensity): 136 (M^+−HOTHP, 37), 111 (38), 83 (72), 55 (63), 41 (100); HRMS Calcd for $C_{15}H_{26}O_2$–$C_5H_{10}O_2$ 136.1252, found: 136.1247.

4.5.2. 2-(1-Cyclohexylhep-6-enyloxy)tetrahydropyran (18d). 89% Yield, TLC R_f=0.82 (hexane/EtOAc=10:1), a mixture of two diastereomers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77–5.82 (m, 1H, C*H*=CH$_2$), 4.90–5.00 (m, 2H, CH=CH_2), 4.63 and 4.59 (br, 1H, O–C*H*–O), 3.89–3.90 (m, 1H, *CH*–OTHP), 3.35–3.47 (m, 2H, CH_2–O–CH), 2.03–2.05 (m, 2H, CH_2–CH=CH$_2$), 1.01–1.81 (m, 23H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.1, 138.9, 114.2, 114.1, 98.9, 97.5, 82.0, 80.6, 62.8, 62.6, 41.4, 40.7, 33.8, 33.7, 31.6, 31.2, 31.1, 29.6, 29.2, 28.9, 28.5, 26.7, 26.5, 26.48, 26.42, 25.6, 25.5, 24.5, 20.1, 19.9; IR (CH_2Cl_2, cm^{-1}): 3076, 2925, 1453, 1114, 1077; MS *m/z* (rel intensity): 281 (M^++1, 4), 197 (M^+−83, 8), 97 (18), 85 (100), 55 (10), 41 (8); HRMS Calcd for $C_{18}H_{32}O_2$ 280.2402, found: 280.2401.

4.5.3. 2-(2-Allylphenoxy)tetrahydropyran (38). 92% Yield, TLC R_f=0.83 (hexane/EtOAc 10=1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09–7.25 (m, 3H, Ph), 6.92–6.95 (m, 1H, Ph), 5.95–6.05 (m, 1H), 5.42 (br t, J=3.2 Hz, 1H), 5.02–5.10 (m, 2H), 3.87–3.90 (m, 1H), 3.59–3.62 (m, 1H), 3.42–3.44 (m, 2H), 1.61–1.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.7, 137.2, 129.8, 129.1, 127.3, 121.3, 115.2, 114.2, 96.1, 61.8, 34.7, 30.5, 25.3, 18.8; IR (CH_2Cl_2, cm^{-1}): 2942, 2875, 1490, 1455, 1355, 1236, 1201, 1125, 1037, 970; MS *m/z* (rel intensity): 218 (M^+, 5), 134 (80), 133 (12), 119 (15), 115 (12), 91 (16), 85 (100), 57 (28); HRMS Calcd for $C_{14}H_{18}O_2$ 218.1307, found: 218.1302.

4.5.4. 3-[2-(Tetrahydropyran-2-yloxy)phenyl]propan-1-ol (44). To a solution of 9-BBN in hexane (0.4 M in hexane, 2.6 mL, 1.04 mmol) was added a solution of alkene **38** (200 mg, 0.92 mmol) in anhydrous benzene (2 mL) dropwise over 20 min while the temperature was maintained under refluxing condition. After stirring under refluxing condition for 2 h, the resulting solution was cooled to 50 °C. To the resulting solution was added a mixture of 6N NaOH (1 mL) and hydrogen peroxide (30 wt% solution in water, 2 mL) dropwise over 5 min and stirred at 50 °C for 1 h. The reaction mixture was cooled to room temperature and saturated aqueous K_2CO_3 (10 mL) was added. The aqueous phase was separated and extracted with ether. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give the alcohol **44** (141 mg, 0.60 mmol) in 65% yield. TLC R_f=0.23 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09–7.17 (m, 3H, Ph), 6.92–6.94 (m, 1H, Ph), 5.41–5.43 (m, 1H), 3.80–3.90 (m, 1H), 3.60–3.64 (m, 3H), 2.74–2.78 (m, 2H), 1.63–1.92 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 130.6, 130.0, 127.0, 121.5, 114.3, 96.4, 62.1, 61.9, 33.0, 30.5, 26.2, 25.1, 19.0; IR (CH_2Cl_2, cm^{-1}): 3366, 2923, 2851, 1594, 1455, 1355, 1235, 1118, 1053, 978, 751; MS *m/z* (rel intensity): 236 (M^+, 2), 152 (60), 134 (58), 107 (38), 85 (100), 67 (28), 57 (30); HRMS Calcd for $C_{14}H_{20}O_3$ 236.1412, found: 236.1410.

4.5.5. 3-[2-(Tetrahydropyran-2-yloxy)phenyl]propionaldehyde (45). To a mixture of alcohol **44** (200 mg, 0.85 mmol), 4 Å molecular sieve (200 mg), and sodium acetate (83.7 mg, 1.02 mmol) in 5 mL of CH_2Cl_2 was added PCC (pyridinium chloroformate, 220 mg, 1.02 mmol) at room temperature. After stirring at room temperature for 2 h, the reaction mixture was concentrated. The crude residue was added 10 mL of ether. The solution was filtered and the chromium salt was washed three times with 5 mL of ether. The combined filtrates were evaporated and the residue was chromatograped on silica gel column to give the aldehyde **45** (141 mg, 0.60 mmol) in 71% yield. TLC R_f=0.55 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.82 (s, 1H, C*H*O), 7.09–7.19 (m, 3H, Ph), 6.89–6.93 (m, 1H, Ph), 5.42–5.44 (m, 1H), 4.81–4.92 (m, 1H), 4.55–4.65 (m, 1H), 2.96–3.00 (m, 2H), 2.75–2.78 (m, 2H), 1.26–1.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.0, 154.7, 129.8, 129.0, 127.5, 121.3, 114.1, 96.1, 62.0, 44.0, 30.4, 25.1, 23.5, 18.9; IR (CH_2Cl_2, cm^{-1}): 3030, 2942, 2875, 1719, 1490, 1237, 1123, 1036, 966, 754; MS *m/z* (rel intensity): 234 (M^+, 4), 166 (12), 152 (18), 150 (24), 134 (24), 85 (100), 67 (16), 57 (16); HRMS Calcd for $C_{14}H_{18}O_3$ 234.1256, found: 234.1248.

4.6. General procedure to prepare the azide from the corresponding alcohol by modified Mitsunobu reaction

To a mixture of alcohol **12c** (1.0 g, 5.90 mmol) and Ph_3P (1.87 g, 7.14 mmol) in 18 mL of THF was subsequently added DEAD (1.24 g, 7.14 mmol) and diphenylphosphonic azide (1.96 g, 7.14 mmol) in the dark at room temperature. After stirring at room temperature for 6 h, the reaction mixture was concentrated and chromatographed on silica gel column to give azido compound **49c** (0.97 g, 5.01 mmol) in 85% yield.

4.6.1. (1-Azidopent-4-enyl)cyclohexane (49c). 85% Yield, TLC R_f=0.86 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.74–5.85 (m, 1H, –C*H*=CH_2), 4.99–5.09 (m, 2H, –CH=C*H*$_2$), 3.08–3.11 (m, 1H, C*H*N_3), 2.13–2.24 (m, 2H, –C*H*$_2$–C=CH_2), 1.07–1.78 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.6, 115.3, 68.0, 42.4, 30.8, 30.6, 29.9, 28.6, 26.3, 26.2, 26.1; IR (CH_2Cl_2, cm^{-1}): 2996, 2094, 1640, 1448, 1088, 910; MS *m*/*z* (rel intensity): 193 (M^+, 3), 192 (20), 138 (30), 95 (25), 83 (47), 67 (31), 55 (100), 41 (67); HRMS Calcd for $C_{11}H_{19}N_3$ 193.1579, found: 193.1577.

4.6.2. (1-Azidohex-5-enyl)cyclohexane (49d). 78% Yield, TLC R_f=0.97 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.77–5.84 (m, 1H, –C*H*=CH_2), 4.96–5.05 (m, 2H, –CH=C*H*$_2$), 3.00–3.10 (m, 1H), 2.08–2.10 (m, 2H), 1.12–1.79 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.3, 114.9, 68.6, 42.3, 33.5, 30.8, 30.0, 28.6, 26.3, 26.2, 26.1, 25.7; IR (CH_2Cl_2, cm^{-1}): 3076, 2928, 2854, 2095, 1640, 1449, 1259, 991, 911, 741; MS *m*/*z* (rel intensity): 207 (M^+, 4), 179 (20), 136 (28), 124 (22), 97 (100), 96 (84), 82 (52), 69 (46), 57 (24), 55 (84); HRMS Calcd for $C_{12}H_{21}N_3$ 207.1735, found: 207.1742.

4.6.3. (1-Cyclohexylhex-5-enyl)carbamic acid methyl ester (53d). To a solution of the azide **49d** (4.0 g, 19.33 mmol) in THF (18 mL) was added a solution of Ph_3P (5.57 g, 21.3 mmol) in 2 mL of THF (2 mL) at 40 °C for 30 min. The resulted solution was added H_2O (0.4 mL, 22 mmol) and stirred at room temperature for 10 h. The resulted solution was treated with K_2CO_3 (3.3 g, 24.4 mmol) in 20 mL of water and stirred for 20 min whereupon methyl chloroformate (2.5 g, 24.4 mmol) was added. After stirring for 1 h, the aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give the benzoate **53d** (2.31 g, 9.67 mmol) in 50% yield. TLC R_f=0.73 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75–5.81 (m, 1H), 4.93–5.03 (m, 2H), 4.38–4.41 (m, 1H), 3.65 (s, 3H), 3.46–3.49 (m, 1H), 2.03–2.07 (m, 2H), 1.50–1.76 (m, 4H), 0.96–1.23 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.0, 138.6, 114.6, 55.6, 51.9, 42.3, 33.6, 31.7, 29.6, 28.1, 26.4, 26.24, 26.22, 25.4; IR (CH_2Cl_2, cm^{-1}): 3321, 2925, 2851, 1698, 1540, 1456, 1255, 649; MS *m*/*z* (rel intensity): 239 (M^+, 5), 170 (31), 156 (100), 114 (28), 88 (45), 81 (49), 76 (56), 55 (15); HRMS Calcd for $C_{14}H_{25}NO_2$ 239.1885, found: 239.1875.

4.7. General procedure to prepare the α-substituted acrolein from terminal alkene

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar is charged with terminal alkene **14b** (400 mg, 1.9 mmol) in CH_2Cl_2 (10 mL). The flask is cooled to −78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. A mixture of Et_2NH (2.94 mL, 28.5 mmol) and CH_2Br_2 (0.67 mL, 9.5 mmol) was heated to 55 °C for 1.5 h to give a yellow solution and then cooled to room temperature. To a solution of ozonide in CH_2Cl_2 generated above was added a preheated mixture of Et_2NH and CH_2Br_2 at −78 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at room temperature. The reaction was complete in 1.5 h and the reaction mixture was concentrated. To the crude mixture, ether was added and most of the ammonium salts were precipitated out. After filtration, the filtrate was concentrated, chromatographed on the silica gel column to give the desired product **15b** (297.9 mg, 1.33 mmol) in 70% yield.

4.7.1. 1-Cyclohexyl-3-formylbut-3-enyl acetate (15b). 70% Yield, TLC R_f=0.6 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.43 (s, 1H, C*H*O), 6.22 (s, 1H, –C=C*H*$_2$), 5.97 (s, 1H, –C=C*H*$_2$), 4.77–4.81 (m, 1H, C*H*OAc), 2.55–2.59 (m, 1H, –C*H*$_2$–C=CH_2), 2.27–2.30 (m, 1H, –C*H*$_2$–C=CH_2), 1.90 (s, 3H, –COC*H*$_3$), 0.98–1.69 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7, 170.4, 146.6, 135.2, 75.5, 41.5, 29.8, 28.8, 27.9, 26.1, 25.8, 25.8, 20.8; IR (CH_2Cl_2, cm^{-1}): 3089, 2853, 1732, 1695, 1452, 988; MS *m*/*z* (rel intensity): 164 (M^+−60, 3), 95 (26), 88 (30), 55 (38), 43 (100); HRMS Calcd for $C_{13}H_{20}O_3$–CH_3CO_2H 164.1201, found: 164.1205.

4.7.2. 1-Cyclohexyl-4-formylhex-4-enyl acetate (15c). 65% Yield, TLC R_f=0.62 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.46 (br s, 1H, C*H*O), 6.22 (s, 1H, –C=C*H*$_2$), 5.95 (s, 1H, –C=C*H*$_2$), 4.67–4.69 (m, 1H, C*H*OAc), 2.00–2.15 (m, 2H, –C*H*$_2$–C=CH_2), 1.99 (s, 3H, –COC*H*$_3$), 0.91–1.68 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.3, 170.8, 149.5, 134.2, 77.0, 41.0, 29.1, 28.8, 28.0, 26.2, 25.9, 25.8, 23.9, 20.9; IR (CH_2Cl_2, cm^{-1}): 3088, 2853, 1731, 1696, 1450, 1085; MS *m*/*z* (rel intensity): 195 (M^+−43, 10), 178 (25), 113 (73), 95 (50), 55 (37); HRMS Calcd for $C_{14}H_{22}O_3$–CH_3CO 195.1385, found: 195.1384.

4.7.3. 1-Cyclohexyl-5-formylhex-5-enyl acetate (15d). 73% Yield; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.53 (s, 1H), 6.24 (s, 1H, C=C*H*$_2$), 5.99 (s, 1H, C=C*H*$_2$), 4.72–4.77 (m, 1H, C*H*OCO), 2.23–2.25 (m, 2H), 2.04 (s, 3H, –COC*H*$_3$), 1.47–1.75 (m, 9H), 1.00–1.18 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 170.9, 149.9, 134.0, 77.5, 41.2, 30.7, 28.9, 28.1, 27.6, 26.3, 26.04, 25.97, 23.7, 21.0; IR (CH_2Cl_2, cm^{-1}): 2929, 2854, 1731, 1696, 1507, 1449, 1371, 1243, 1020, 963, 733; MS *m*/*z* (rel intensity): 192 (M^+−60, 24), 109 (44), 95 (40), 81 (100), 67 (36), 55 (56); HRMS Calcd for $C_{15}H_{24}O_3$–HOAc 192.1514, found: 192.1516.

4.7.4. 2-[Cyclohexyl(tetrahydropyran-2-yloxy)methyl]-propenal (19a). 58% Yield, TLC R_f=0.65 (hexane/EtOAc=10:1); A mixture of two diastereomers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.55 (s, 0.6H, C*H*O), 9.50 (s, 0.4H, C*H*O), 6.44 (s, 0.4H, –C=C*H*$_2$), 6.27 (s, 0.6H, –C=C*H*$_2$),

6.13 (s, 0.6H, –C═CH_2), 6.08 (s, 0.4H, –C═CH_2), 4.21–4.43 (m, 2H, O–CH–O), 3.82–3.87 (m, 1H), 3.41–3.44 (m, 1H, CH_2–O–CH), 1.44–1.83 (m, 17H), 0.87–1.21 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.5, 193.2, 150.6, 149.2, 134.9, 100.9, 95.3, 78.1, 74.9, 63.0, 62.1, 42.2, 42.0, 30.6, 30.5, 29.6, 29.5, 29.2, 28.1, 27.7, 26.34, 26.32, 26.14, 26.07, 25.97, 25.92, 25.35, 25.24, 19.8, 19.3; IR (CH_2Cl_2, cm^{-1}): 2997, 2853, 1689, 1450, 1024, 971; MS *m/z* (rel intensity): 151 (M^+−OTHP, 6), 84 (46), 67 (20), 55 (58), 41 (100); HRMS Calcd for $C_{15}H_{24}O_3$–$C_5H_9O_2$ 151.1123, found: 151.1114.

4.7.5. 2-[4-Cyclohexyl-4-(tetrahydropyran-2-yloxy)-butyl]propenal (19d). 76% Yield, TLC R_f=0.69 (hexane/EtOAc=10:1); A mixture of the diastereomers, ratio=1:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, CHO), 6.23 (s, 0.5H, C═CH_2), 6.21 (s, 0.5H, C═CH_2), 5.96 (s, 1H, C═CH_2), 4.57–4.58 (m, 1H, O–CH–O), 4.52–4.59 (m, 1H, O–CH–O), 3.84–3.86 (m, 1H, CH_2–O–CH), 3.34–3.44 (m, 2H, CH–OTHP), 2.19–2.20 (m, 2H, CH_2–C═CH_2), 1.43–1.71 (m, 16H), 0.94–1.21 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.6, 194.5, 150.3, 150.2, 133.83, 133.81, 99.1, 97.6, 81.7, 80.4, 62.9, 62.6, 41.4, 40.8, 31.2, 31.1, 29.0, 28.7, 28.5, 28.4, 27.9, 27.7, 26.6, 26.39, 26.37, 26.35, 26.32, 25.5, 25.4, 23.6, 20.2, 19.8; IR (CH_2Cl_2, cm^{-1}): 3085, 2923, 1693, 1451, 1029; MS *m/z* (rel intensity): 276 (M^+−18, 8), 211 (10), 175 (21), 85 (100), 41 (22); HRMS Calcd for $C_{18}H_{30}O_3$ 294.2195, found: 294.2196.

4.7.6. 3-Formyl-1-methyl-1-phenylbut-3-enyl acetate (26a). 73% Yield, TLC R_f=0.45 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (s, 1H, CHO), 7.21–7.32 (m, 5H, Ph–H), 6.06 (s, 1H, –C═CH_2), 6.04 (s, 1H, C═CH_2), 2.95 (s, 2H, –CH_2–C═CH_2), 2.03 (s, 3H, –COCH_3), 1.79 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.5, 169.1, 144.8, 143.7, 137.7, 128.0, 127.0, 124.5, 82.8, 39.0, 24.3, 22.9; IR (CH_2Cl_2, cm^{-1}): 3026, 2937, 1736, 1687, 1496, 1016, 735; MS *m/z* (rel intensity): 173 (M^+−59, 8), 172 (40), 143 (81), 128 (72), 121 (100).

4.7.7. 4-Formyl-1-methyl-1-phenylpent-4-enyl acetate (26b). 81% Yield, TLC R_f=0.47 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.44 (s, 1H, CHO), 7.20–7.31 (m, 5H), 6.14 (s, 1H, –C═CH_2), 5.90 (s, 1H, –C═CH_2), 2.12–2.17 (m, 4H), 2.05 (s, 3H, –COCH_3), 1.86 (s, 3H, –CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.0, 169.2, 149.3, 144.2, 133.6, 128.0, 126.7, 124.2, 83.1, 39.9, 24.6, 22.0, 21.8; IR (CH_2Cl_2, cm^{-1}): 3027, 2845, 1731, 1629, 1496, 1016, 735; MS *m/z* (rel intensity): 246 (M^+, 4), 186 (18), 163 (22), 121 (71), 43 (100).

4.7.8. 1-(2-Formylallyl)cyclohexyl acetate (26c). 62% Yield, TLC R_f=0.45 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, CHO), 6.25 (s, 1H, –C═CH_2), 6.10 (s, 1H, –C═CH_2), 2.87 (s, 2H, –CH_2–C═CH_2), 2.06–2.09 (m, 2H), 1.97 (s, 3H, –COCH_3), 1.19–1.51 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 170.6, 145.8, 137.6, 82.9, 34.5, 34.2, 25.2, 22.3, 21.6; IR (CH_2Cl_2, cm^{-1}): 2997, 2933, 2860, 1730, 1696, 1449, 1368, 964, 920; MS *m/z* (rel intensity): 164 (M^+−46, 24), 99 (100), 94 (38), 84 (42), 43 (83); HRMS Calcd for $C_{12}H_{18}O_3$ 210.1256, found: 210.1253.

4.7.9. 1-(3-Formylbut-3-enyl)cyclohexyl acetate (26d). 85% Yield, TLC R_f=0.5 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H, CHO), 6.19 (s, 1H, –C═CH_2), 5.92 (s, 1H, –C═CH_2), 2.12–2.16 (m, 4H), 1.94 (s, 3H, –COCH_3), 1.92–1.96 (m, 2H), 1.18–1.46 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.3, 170.1, 149.9, 133.7, 83.2, 35.2, 34.3, 25.4, 22.0, 21.6, 21.2; IR (CH_2Cl_2, cm^{-1}): 3086, 2934, 2860, 1731, 1690, 1450, 1367, 1041; MS *m/z* (rel intensity): 165 (M^+−59, 44), 164 (100), 146 (50), 99 (76), 43 (88); HRMS Calcd for $C_{13}H_{20}O_3$ 224.1412, found: 224.1405.

4.7.10. *trans*-2-(1-Formylvinyl)cyclohexyl acetate (34a). 76% Yield, TLC R_f=0.45 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.44 (s, 1H, CHO), 6.21 (s, 1H, –C═CH_2), 5.95 (s, 1H, –C═CH_2), 4.79–4.84 (m, 1H, CHOAc), 2.67–2.72 (m, 1H, –CH–C═CH_2), 1.19–2.00 (m, 8H), 1.87 (s, 3H, –COCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.9, 170.3, 151.3, 133.7, 74.3, 40.5, 31.93, 31.86, 25.3, 24.4, 20.9; IR (CH_2Cl_2, cm^{-1}): 3090, 2996, 1733, 1633, 1455, 1373, 1024; MS *m/z*(rel intensity): 196 (M^+, 3), 169 (41), 136 (38), 124 (56), 109 (100), 81 (78), 67 (54); HRMS Calcd for $C_{11}H_{16}O_3$ 196.1099, found: 196.1094.

4.7.11. *trans*-2-(2-Formylallyl)cyclohexyl acetate (34b). 69% Yield, TLC R_f=0.47 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.44 (s, 1H, CHO), 6.23 (s, 1H, –C═CH_2), 5.97 (s, 1H, –C═CH_2), 4.84–4.90 (m, 1H, CHOAc), 2.58–2.61 (m, 1H, –CH_2–C═CH_2), 2.17–2.31 (m, 1H, –CH_2–C═CH_2), 1.95–2.05 (m, 1H), 1.91 (s, 3H, –COCH_3), 1.23–1.96 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.7, 170.5, 146.3, 135.3, 75.3, 43.7, 31.9, 28.9, 28.5, 25.4, 25.2, 20.9; IR (CH_2Cl_2, cm^{-1}): 3091, 2952, 1732, 1692, 1452, 1372, 946; MS *m/z* (rel intensity): 167 (M^+−43, 32), 166 (29), 81 (28), 43 (100), 41 (27); HRMS Calcd for $C_{12}H_{18}O_3$–CH_3CO 167.1072, found: 167.1081.

4.7.12. *cis*-2-(1-Formylvinyl)cyclohexyl benzoate (34c). 71% Yield, TLC R_f=0.6 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.47 (s, 1H, CHO), 8.00–8.02 (m, 2H, Ph–H), 7.54–7.57 (m, 1H), 7.27–7.46 (m, 2H), 6.22 (s, 1H, –C═CH_2), 5.94 (s, 1H, –C═CH_2), 5.38 (br s, 1H, CHOCOPh), 2.90–2.94 (br d, J=12.8 Hz, 1H, –CH–C═CH_2), 1.56–2.05 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.4, 165.9, 151.4, 135.0, 133.2, 131.1, 129.8, 128.8, 70.9, 38.6, 30.9, 26.0, 25.2, 20.8; IR (CH_2Cl_2, cm^{-1}): 3032, 2859, 1715, 1707, 1450, 1069; MS *m/z* (rel intensity): 258 (M^+, 12), 240 (18), 136 (10), 105 (100), 77 (16); HRMS Calcd for $C_{16}H_{18}O_3$ 258.1256, found: 258.1259.

4.7.13. *cis*-2-(2-Formylallyl)cyclohexyl benzoate (34d). 64% Yield, TLC R_f=0.63 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.51 (s, 1H, CHO), 7.99–8.02 (m, 2H), 7.53–7.56 (m, 1H), 7.41–7.45 (m, 2H), 6.29 (s, 1H, –C═CH_2), 5.98 (s, 1H, –C═CH_2), 5.22–5.26 (m, 1H, CHOCOPh), 2.55–2.76 (m, 2H, –CH_2–C═CH_2), 1.27–2.20 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.3, 166.5, 146.7, 136.1, 133.2, 130.9, 129.9, 128.7, 76.5, 44.6, 32.5, 29.5, 28.9, 26.0, 25.8; IR (CH_2Cl_2, cm^{-1}): 3033, 2869, 1714, 1629, 1451, 1070; MS *m/z* (rel intensity): 273 (M^++1, 12), 243 (M^+−29, 12), 203 (5), 150 (7), 105

(100), 77 (21); HRMS Calcd for $C_{17}H_{20}O_3$ 272.1412, found: 272.1406.

4.7.14. 2-[2-(Tetrahydropyran-2-yloxy)phenyl]propenal (39). 52% Yield, TLC R_f=0.5 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.76 (s, 1H), 7.18–7.34 (m, 3H), 6.99–7.03 (m, 1H), 6.34 (s, 1H, C=CH_2), 6.28 (s, 1H, C=CH_2), 5.42 (br t, 1H), 3.83–3.89 (m, 1H), 3.59–3.63 (m, 1H), 1.56–1.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2, 154.4, 147.4, 132.9, 130.3, 130.1, 124.8, 121.5, 114.7, 96.5, 61.8, 30.2, 25.2, 18.4; IR (CH_2Cl_2, cm^{-1}): 2943, 2870, 1701, 1597, 1488, 1454, 1236, 1201, 1111, 1036, 961, 919; MS *m*/*z* (rel intensity): 232 (M^+, 1), 148 (55), 147 (8), 85 (100), 91 (15), 77 (4), 57 (16); HRMS Calcd for $C_{14}H_{16}O_3$ 232.1099, found: 232.1102.

4.7.15. 2-[2-(Tetrahydropyran-2-yloxy)benzyl]propenal (46). 62% Yield, TLC R_f=0.69 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.65 (s, 1H, C*H*O), 7.14–7.21 (m, 3H, Ph), 6.95–6.97 (m, 1H, Ph), 6.04 (br s, 2H), 5.42 (br s, 1H), 3.82–3.85 (m, 1H), 3.62 (s, 3H), 1.29–1.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.0, 154.9, 149.3, 134.5, 130.9, 127.9, 127.0, 121.3, 114.3, 96.2, 61.9, 30.4, 28.5, 25.2, 18.7; IR (CH_2Cl_2, cm^{-1}): 2942, 2869, 2851, 1693, 1490, 1455, 1238, 1202, 1121, 1036, 967, 922, 872, 754; MS *m*/*z* (rel intensity): 246 (M^+, 1), 162 (56), 85 (100); HRMS Calcd for $C_{15}H_{18}O_3$ 246.1256, found:. 246.1262.

4.7.16. 2-(2-Azido-2-cyclohexylethyl)propenal (50c). 62% Yield, TLC R_f=0.7 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.55 (s, 1H, CHO), 6.42 (s, 1H, –C=CH_2), 6.15 (s, 1H, –C=CH_2), 3.26–3.29 (m, 1H, C*H*N_3), 2.59–2.64 (m, 1H, –CH_2–C=CH_2), 2.24–2.30 (m, 1H, –CH_2–C=CH_2), 1.09–1.78 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.1, 146.7, 136.8, 66.2, 42.7, 30.6, 29.8, 28.4, 26.2, 26.1, 25.9; IR (CH_2Cl_2, cm^{-1}): 2928, 2853, 2095, 1698, 1449, 1089; MS *m*/*z* (rel intensity): 207 (M^+, 5), 178 (21), 162 (18), 110 (22), 86 (37), 84 (54), 55 (43), 49 (100); HRMS Calcd for $C_{11}H_{17}N_3O$ 207.1372, found: 207.1374.

4.7.17. (1-Cyclohexyl-4-formylpent-4-enyl)carbamic acid methyl ester (54d). 65% Yield, TLC R_f=0.77 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H, C*H*O), 6.28 (br s, 1H, –CH=CH_2), 5.99 (br s, 1H, –C=CH_2), 4.51–4.55 (m, 1H, NH), 3.64 (s, 3H, OCH_3), 3.43–3.46 (m, 1H, NC*H*), 2.18–2.52 (m, 3H), 1.01–1.72 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 157.0, 149.6, 134.6, 55.2, 51.9, 42.2, 30.4, 29.5, 28.1, 26.3, 26.1, 25.9; IR (CH_2Cl_2, cm^{-1}): 3323 (NH), 2925, 1698, 1540, 1456; MS *m*/*z* (rel intensity): 253 (M^+, 1), 252 (M^+-1, 2), 170 (40), 116 (100), 109 (38); HRMS Calcd for $C_{14}H_{23}NO_3$ 253.1678, found: 253.1676.

4.8. General procedure to prepare the α-substituted acrylic acid from the corresponding α-substituted acrolein

To a solution of aldehyde **4a** (2.57 g, 16.64 mmol) in 60 mL of *t*-butyl alcohol and 5.3 mL of 2-methyl-2-butene (3.50 g, 49.93 mmol) was added a solution of sodium chlorite (3.46 g, 38.28 mmol) and sodium dihydrogenphosphate (5.19 g, 33.29 mmol) in 22 mL of water dropwise over a 10 min period. The pale yellow reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 30 mL of water and this extracted with 100 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 50 mL portions of ether. The combined ether layers were washed with 50 mL of water, dried with Na_2SO_4, concentrated and chromatographed on silica gel column to give product **7a** (2.77 g, 16.31 mmol) in 98% yield.

4.8.1. 2-Heptylacrylic acid (7a). 98% Yield; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.11 (br, 1H, CO_2H), 6.27 (s, 1H, C=CH_2), 5.63 (s, 1H, C=CH_2), 2.29 (t, *J*=7.3 Hz, 2H, –CH_2(C=CH_2)–), 1.37–1.51 (m, 2H), 1.17–1.37 (m, 8H), 0.88 (t, *J*=7.1 Hz, 3H, –CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.0, 140.4, 126.7, 31.8, 31.5, 29.2, 29.1, 28.4, 22.6, 14.0; IR (CH_2Cl_2, cm^{-1}): 2500–3250 (OH), 1690 (C=O), 1625, 1437, 1160, 948; MS *m*/*z* (rel intensity): 170 (M^+, 6), 152 (10), 113 (13), 97 (42), 87 (100), 69 (35); HRMS Calcd for $C_{10}H_{18}O_2$ (M^+) 170.1307, found 170.1313.

4.8.2. 2-(3-Oxocyclohexyl)acrylic acid (7b). 83% Yield; white solid, mp 80–81 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.42 (s, 1H, C=CH_2), 5.70 (s, 1H, C=CH_2), 2.97 (t, *J*=10.9 Hz, 1H), 2.20–2.60 (m, 4H), 1.98–2.15 (m, 2H), 1.55–1.85 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.8, 171.4, 142.5, 126.5, 46.4, 41.1, 39.4, 30.4, 24.8; IR (CH_2Cl_2, cm^{-1}): 2500–3550 (OH), 1689 (C=O), 1622, 1416, 1284, 1152; MS *m*/*z* (rel intensity): 168 (M^+, 8), 150 (10), 125 (8), 109 (4), 95 (4), 62 (46), 45 (100).

4.8.3. 2-(1,1-Dimethyl-3-oxobutyl)acrylic acid (7c). 72% Yield; red brown oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.31 (s, 1H, C=CH_2), 5.73 (s, 1H, C=CH_2), 2.91 (s, 2H, –CH_2C=O), 2.08 (s, 3H, CH_3CO), 1.27 (s, 6H, C(CH_3)$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.3, 172.3, 146.2, 125.9, 53.0, 36.7, 31.6, 28.2; IR (CH_2Cl_2, cm^{-1}): 2500–3550 (OH), 1714 (C=O), 1611, 1358, 1305, 1258, 1138, 1104; MS *m*/*z* (rel intensity): 170 (M^+, 6), 152 (18), 137 (22), 124 (16), 109 (22), 95 (40), 81 (20), 67 (38), 43 (100); HRMS Calcd for $C_9H_{14}O_3$ 170.0943, found 170.0949.

4.8.4. 2-(8-Hydroxyoctyl)acrylic acid (7d). 85% Yield; white solid, mp 32 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25 (s, 1H, C=CH_2), 5.61 (s, 1H, C=CH_2), 3.63 (t, *J*=6.6 Hz, 2H, –CH_2OH), 2.29 (t, *J*=7.4 Hz, 2H, –CH_2(C=CH_2)–), 1.25–1.55 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.8, 140.4, 126.2, 62.7, 32.4, 31.4, 29.2, 29.0, 28.3, 25.6; IR (CH_2Cl_2, cm^{-1}): 3418 (OH), 1717 (C=O), 1629, 1436, 1195, 1162, 1052, 943; MS *m*/*z* (rel intensity): 183 (M^+-OH, 4), 137 (15), 108 (10), 92 (72), 91 (100), 81 (9), 69 (10), 55 (12).

4.8.5. 2-(8-Acetoxyoctyl)acrylic acid (7e). 98% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.27 (s, 1H, C=CH_2), 5.63 (s, 1H, C=CH_2), 4.06 (t, *J*=6.8 Hz, 2H, –CH_2(C=CH_2)–), 2.29 (t, *J*=7.3 Hz, 2H), 2.04 (s, 3H, $OCOCH_3$), 1.30–1.65 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.5, 171.3, 126.7, 64.6, 31.4, 29.2, 29.1, 28.6, 28.3, 25.9, 21.0; IR (CH_2Cl_2, cm^{-1}): 1690 (C=O), 1625, 1437, 1160, 1160, 948; MS *m*/*z* (rel intensity): 242

(M^+, 2), 224 (2), 209 (5), 137 (15), 91 (100), 81 (15), 69 (11), 55 (13), 43 (20); HRMS Calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1398.

4.8.6. 2-(8-Iodooctyl)acrylic acid (7f). 98% Yield; yellow solid, mp 32 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.29 (s, 1H, C═CH_2), 5.64 (s, 1H, C═CH_2), 3.18 (t, J=7.1 Hz, 2H, −CH_2I), 2.29 (t, J=7.3 Hz, 2H, −CH_2(C═CH_2)−), 1.82 (quin, J=6.9 Hz, 2H), 1.32–1.51 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 140.2, 126.9, 33.5, 31.4, 30.5, 29.1, 29.0, 28.4, 28.3, 7.1; IR (CH_2Cl_2, cm^{-1}): 2500–3450 (OH), 1687 (C═O), 1624; MS *m*/*z* (rel intensity): 310 (M^+, 3), 283 (6), 183 (15), 137 (48), 91 (100), 81 (48), 69 (25), 55 (45), 41 (38); HRMS Calcd for $C_{11}H_{19}IO_2$ (M^+) 310.0430, found 310.0414.

4.8.7. 3-Cyclohexyl-2-methylene-3-(tetrahydropyran-2-yloxy)propionic acid (20a). 93% Yield, TLC R_f=0.4 (hexane/EtOAc=1:1); A mixture of the diastereomers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.46 (s, 0.6H, C═CH_2), 6.42 (s, 0.4H, C═CH_2), 5.91 (s, 0.4H, C═CH_2), 5.79 (s, 0.6H, C═CH_2), 4.63–4.64 (m, 0.4H, O−CH−O), 4.55–4.56 (m, 0.6H, O−CH−O), 4.37–4.39 (m, 0.6H, *CH*−OTHP), 4.17–4.19 (m, 0.4H, CH−OTHP), 3.80–3.95 (m, 0.6H, CH_2−O−CH), 3.65–3.75 (m, 0.4H, CH_2−O−CH), 3.50–3.53 (m, 0.6H, CH_2−O−CH), 3.45–3.55 (m, 0.4H, CH_2−O−CH), 0.95–2.00 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.96, 170.92, 140.7, 139.4, 128.6, 127.9, 100.7, 94.9, 80.8, 77.1, 62.7, 62.0, 42.5, 42.2, 30.6, 30.4, 29.7, 29.4, 28.3, 27.9, 26.4, 26.4, 26.2, 26.1, 26.0, 25.9, 25.4, 25.3, 19.5, 19.1; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 1715, 1450, 1028, 734; MS *m*/*z* (rel intensity): 268 (M^+, 3), 185 (66), 167 (90), 85 (100), 55 (14); HRMS Calcd for $C_{15}H_{24}O_4$ 268.1675, found: 268.1685.

4.8.8. 6-Cyclohexyl-2-methylene-6-(tetrahydropyran-2-yloxy)hexanoic acid (20d). 91% Yield, TLC R_f=0.40 (hexane/EtOAc=1:1). A mixture of the diastereomers, ratio=1:1; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.28 (s, 1H, C═CH_2), 5.64–5.65 (m, 1H, C═CH_2), 4.59–4.65 (m, 1H, O−CH−O), 3.90–3.91 (m, 1H, CH_2−O−CH), 3.39–3.50 (m, 2H, CH_2−O−CH), 2.29–2.31 (m, 2H, CH_2−C═CH_2), 1.48–1.75 (m, 16H), 0.88–1.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.3, 172.2, 140.2, 140.1, 126.8, 126.7, 99.0, 97.7, 81.7, 80.6, 62.9, 62.7, 41.5, 40.87, 40.86, 31.7, 31.5, 31.2, 31.1, 29.4, 29.1, 28.7, 28.6, 28.4, 26.7, 26.4, 25.5, 24.2, 23.8, 20.1, 19.9; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 2853, 1697, 1626, 1453, 1132, 952; MS *m*/*z* (rel intensity): 209 (M^+−101, 7), 163 (8), 143 (11), 85 (100), 67 (8); HRMS Calcd for $C_{18}H_{30}O_4$ 310.2144, found: 310.2150.

4.9. General procedure to prepare the methyl acrylate from the corresponding acrylic acid

To a solution of α-substituted acrylic acid **7a** (287.2 mg, 1.69 mmol) in 3 mL of CH_2Cl_2 was added a solution of CH_2N_2 in ethyl ether at room temperature. The progress of the reaction should be monitored carefully by TLC. Excess of the CH_2N_2 will cause the further 1,3-dipolar cycloaddition on the double bond. When the reaction was complete, the reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **8a** (304 mg, 1.66 mmol) in 98% yield.

4.9.1. Methyl 2-heptylacrylate (8a). 98% Yield; colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (s, 1H, C═CH_2), 5.51 (s, 1H, C═CH_2), 3.75 (s, 3H, OCH_3), 2.29 (t, J=7.3 Hz, 2H, −CH_2(C═CH_2)−), 1.40–1.68 (m, 2H), 1.21–1.40 (m, 8H), 0.88 (t, J=6.9 Hz, 3H, −CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 140.9, 124.3, 51.6, 31.9, 31.8, 29.1, 29.0, 28.4, 22.6, 14.0; IR (CH_2Cl_2, cm^{-1}): 1718 (C═O), 1629, 1435, 1192, 1148, 940; MS *m*/*z* (rel intensity): 184 (M^+, 8), 153 (12), 127 (20), 101 (100), 88 (58), 81 (18), 69 (30); HRMS Calcd for $C_{11}H_{20}O_2$ 184.1463, found 184.1461.

4.9.2. Methyl 2-(3-oxocyclohexyl)acrylate (8b). 96% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.24 (s, 1H, C═CH_2), 5.57 (s, 1H, C═CH_2), 3.77 (s, 3H, OCH_3), 2.88–3.05 (m, 1H), 2.25–2.50 (m, 4H), 2.00–2.15 (m, 2H), 1.53–1.80 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 210.5, 166.9, 143.2, 124.0, 51.9, 46.5, 41.1, 39.7, 30.4, 24.8; IR (CH_2Cl_2, cm^{-1}): 1705 (C═O), 1626, 1436, 1285, 1144; MS *m*/*z* (rel intensity): 182 (M^+, 42), 150 (100), 139 (32), 122 (52), 108 (22), 95 (36), 79 (44), 67 (34), 53 (38), 41 (50); HRMS Calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0933.

4.9.3. Methyl 2-(1,1-dimethyl-3-oxobutyl)acrylate (8c). 86% Yield; yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.10 (s, 1H, C═CH_2), 5.62 (s, 1H, C═CH_2), 3.73 (s, 3H, OCH_3), 2.89 (s, 2H, −CH_2C═O), 2.05 (s, 3H, CH_3CO), 1.25 (s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.9, 167.8, 147.0, 123.4, 53.1, 51.5, 36.9, 31.6, 28.1; IR (CH_2Cl_2, cm^{-1}): 1709 (C═O), 1614, 1434, 1357, 1316, 1258, 945; MS *m*/*z* (rel intensity): 184 (M^+, 2), 152 (4), 127 (5), 95 (4), 81 (3), 67 (3), 62 (48), 45 (100); HRMS Calcd for $C_{10}H_{16}O_3$ 184.1099, found 184.1100.

4.9.4. Methyl 2-(8-hydroxyoctyl)acrylate (8d). 91% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (s, 1H, C═CH_2), 5.51 (s, 1H, C═CH_2), 4.03 (s, 3H, OCH_3), 3.63 (t, J=6.6 Hz, 2H, −CH_2OH), 2.29 (t, J=7.3 Hz, 2H, −CH_2(C═CH_2)−), 1.20–1.60 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.9, 140.8, 124.4, 63.0, 51.7, 32.7, 31.8, 29.3, 29.1, 28.3, 25.7; IR (CH_2Cl_2, cm^{-1}): 3418 (OH), 1717 (C═O), 1436, 1262, 1195, 1162, 1052, 943; MS *m*/*z* (rel intensity): 214 (M^+, 1), 182 (18), 154 (14), 125 (10), 101 (100), 81 (55), 67 (55), 55 (88), 41 (53).

4.9.5. Methyl 2-(8-acetoxyoctyl)acrylate (8e). 87% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (br s, 2H, OH and ═CH_2), 5.51 (s, 1H, C═CH_2), 4.05 (t, J=4.7 Hz, 2H, AcOCH_2), 3.75 (s, 3H, CO_2CH_3), 2.29 (t, J=7.0 Hz, −CH_2(C═CH_2)−), 2.03 (s, 3H, OCOCH_3), 1.25–1.65 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 167.8, 140.8, 124.4, 64.5, 51.6, 31.8, 29.2, 29.1, 29.0, 28.5, 28.3, 25.8, 20.9; IR (CH_2Cl_2, cm^{-1}): 1721 (C═O), 1628, 1437, 1234, 1037, 940, 815; MS *m*/*z* (rel intensity): 256 (M^+, 1), 224 (38), 182 (35), 164 (28), 136 (28), 125 (18), 101 (52), 95 (32), 81 (55), 67 (56), 55 (80), 43 (100); HRMS Calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1659.

4.9.6. Methyl 2-(8-iodooctyl)acrylate (8f). 87% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.12 (s, 1H, C═CH_2), 5.52 (s, 1H, C═CH_2), 3.75 (s, 3H, OCH_3), 3.18 (t, J=7.1 Hz, 2H, −CH_2I), 2.29 (t, J=7.2 Hz, 2H,

$-CH_2(C{=}CH_2)-$), 1.82 (quin, J=6.9 Hz, 2H), 1.31–1.48 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 140.8, 124.4, 51.7, 33.5, 31.8, 30.4, 29.1, 29.0, 28.4, 28.3, 7.1; IR (CH_2Cl_2, cm^{-1}): 1716 (C=O), 1628, 1435, 1194, 1155, 945; MS *m/z* (rel intensity): 324 (M^+, 8), 293 (12), 197 (43), 165 (32), 137 (100), 109 (18), 95 (65), 81 (82), 67 (48), 55 (65), 41 (45); HRMS Calcd for $C_{12}H_{21}IO_2$ 324.0586, found 324.0584.

4.10. General procedure to prepare the acrylic amide from the corresponding acrylic acid

To a solution of α-substituted acrylic acid **7a** (522.9 mg, 3.07 mmol) in 10 mL of CH_2Cl_2 was added thionyl chloride (1.10 g, 9.21 mmol). The reaction mixture was refluxed for 3 h and then concentrated in vacuo. The residue was redissolved in 10 mL of CH_2Cl_2 and the resulted solution was treated with 28% aqueous NH_3 solution at 0 °C and stirred for 30 min. The reaction mixture was added 20 mL of water and extracted with CH_2Cl_2. The combined organic layer was washed with 50 mL of water, dried with Na_2SO_4 and concentrated. The crude mixture was chromatographed on silica gel column to give acrylic amide **10g** (462 mg, 2.73 mmol) in 89% yield.

4.10.1. 2-Heptylacrylamide (10g). 89% Yield; white solid, mp 70–71 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.82 (br, 1H, NH_2), 5.68 (s, 1H, C=CH_2), 5.33 (s, 1H, C=CH_2), 2.30 (t, J=9.5 Hz, 2H, $-CH_2(C{=}CH_2)-$), 1.40–1.51 (m, 2H), 1.20–1.34 (m, 8H), 0.88 (t, J=6.5 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.9, 144.7, 118.5, 32.2, 31.8, 29.2, 29.1, 28.1, 22.6, 14.0; IR (CH_2Cl_2, cm^{-1}): 3528 (N–H), 3409 (N–H), 1673 (C=O), 1623, 1580, 1375; MS *m/z* (rel intensity): 169 (M^+, 3), 112 (12), 98 (6), 86 (10), 62 (46), 45 (100).

4.10.2. 2-Heptyl-1-(pyrrolidin-1-yl)prop-2-en-1-one (10h). 83% Yield; pale yellow oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.19 (s, 1H, C=CH_2), 5.11 (s, 1H, C=CH_2), 2.30 (t, J=7.3 Hz, 2H, $-CH_2(C{=}CH_2)-$), 1.85–1.93 (m, 4H, 2x$-NCH_2$), 1.40–1.50 (m, 2H), 1.21–1.35 (m, 8H), 0.88 (t, J=6.8 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.6, 146.6, 114.2, 48.6, 45.3, 33.7, 31.7, 29.2, 29.0, 27.6, 26.1, 24.3, 22.5, 13.9; IR (CH_2Cl_2, cm^{-1}): 1614 (C=O), 1438, 912; MS *m/z* (rel intensity): 223 (M^+, 42), 208 (12), 194 (10), 180 (13), 166 (50), 152 (42), 138 (100), 126 (36), 98 (28), 70 (42); HRMS Calcd for $C_{14}H_{25}NO$ 223.1936, found 223.1932.

4.10.3. *N*-(2-*n*-Heptylacryloyl))valine methyl ester (10i). 89% Yield; pale yellow oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.27 (br d, J=8.6 Hz, 1H, NH), 5.66 (s, 1H, C=CH_2), 5.31 (s, 1H, C=CH_2), 4.64 (d, J=11.7 Hz, 0.5H), 4.62 (d, J=11.7 Hz, 0.5 H), 3.76 (s, 3H, OCH_3), 2.18–2.40 (m, 3H), 1.40–1.51 (m, 2 H), 1.20–1.40 (m, 8H), 0.85–0.98 (m, 9H, 3xCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.6, 168.7, 145.5, 117.7, 56.9, 52.1, 32.3, 31.7, 31.4, 29.1, 29.0, 28.0, 22.6, 19.0, 17.8, 14.0; IR (CH_2Cl_2, cm^{-1}): 3332 (N–H), 1744 (C=O), 1659 (C=O), 1620, 1509, 1203; MS *m/z* (rel intensity): 283 (M^+, 10), 252 (6), 224 (100), 170 (46), 153 (65), 69 (18), 55 (39), 41 (40); HRMS Calcd for $C_{16}H_{29}NO_3$ 283.2147, found 283.2134.

4.11. General procedure to prepare the methyl acrylate from the corresponding acrolein in one flask

To a mixture of aldehyde **15b** (324 mg, 1.0 mmol), *t*-butyl alcohol (3.6 mL) and 2-methyl-2-butene (210 mg, 3.0 mmol) was added a solution of sodium chlorite (208 mg, 2.30 mmol) and sodium dihydrogenphosphate (312 mg, 2.0 mmol) in 1.3 mL of water dropwise over a 10 min period. The pale yellow reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated, redissolved in 3 mL of water and extracted with 10 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 15 mL portions of ether. The combined ether layers were washed with 10 mL of water, dried with Na_2SO_4 and concentrated to give the crude product of the acrylic acid. To a solution of the crude acrylic acid in 3 mL of CH_2Cl_2 was added a solution of CH_2N_2 in ethyl ether at room temperature. When the reaction was complete, the reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **16b** (241 mg, 0.95 mmol) in 95% yield.

4.11.1. 4-Acetoxy-4-cyclohexyl-2-methylenebutyric acid methyl ester (16b). 95% Yield, ^1H NMR ($CDCl_3$, 400 MHz) δ 6.11 (br s, 1H, C=CH_2), 5.51 (br s, 1H, C=CH_2), 4.85–4.90 (m, 1H, C*H*OCO), 3.71 (s, 3H, OCH_3), 2.65–2.69 (m, 1H, CH_2–C=CH_2), 2.27–2.33 (m, 1H, CH_2–C=CH_2), 1.93 (s, 3H, $-COCH_3$), 1.00–1.71 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 167.1, 137.2, 126.7, 75.8, 51.8, 41.5, 34.4, 28.9, 28.0, 26.3, 25.91, 25.87, 20.8; IR (CH_2Cl_2, cm^{-1}): 2928, 2857, 1730, 1650, 1237; MS *m/z* (rel intensity): 223 (M^+-31, 4), 141 (43), 95 (100), 83 (41), 58 (43); HRMS Calcd for $C_{14}H_{22}O_4-OCH_3$ 223.1334, found: 223.1324.

4.11.2. 5-Acetoxy-5-cyclohexyl-2-methylenepentanoic acid methyl ester (16c). 93% Yield, TLC R_f=0.65 (hexane/EtOAc=10:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.09 (s, 1H, C=CH_2), 5.49 (s, 1H, C=CH_2), 4.68–4.73 (m, 1H, C*H*OCO), 3.70 (s, 3H, OCH_3), 2.24–2.27 (m, 2H, CH_2–C=CH_2), 2.00 (s, 3H, $-COCH_3$), 1.60–1.71 (m, 9H), 0.93–1.17 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 167.3, 139.9, 124.9, 77.2, 51.6, 41.1, 29.9, 28.8, 28.1, 28.0, 26.3, 26.0, 25.9, 21.0; IR (CH_2Cl_2, cm^{-1}): 2919, 2850, 1735, 1636, 1264; MS *m/z* (rel intensity): 225 (M^+-43), 208 (10), 177 (6), 149 (M^+-119, 25), 143 (28), 111 (32), 43 (100), 32 (95); HRMS Calcd for $C_{15}H_{24}O_4$ 268.1675, found: 268.1682.

4.11.3. 2-(4-Acetoxy-4-cyclohexylbutyl)acrylic acid methyl ester (16d). 96% Yield, ^1H NMR ($CDCl_3$, 400 MHz) δ 6.14 (s, 1H, C=CH_2), 5.52 (s, 1H, C=CH_2), 4.73–4.77 (m, 1H, C*H*OCO), 3.75 (s, 3H), 2.25–2.30 (m, 2H), 2.05 (s, 3H, $-COCH_3$), 1.44–1.75 (m, 10H), 0.97–1.16 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.8, 167.5, 140.3, 124.8, 77.5, 51.6, 41.2, 31.6, 30.6, 28.9, 28.1, 26.3, 26.04, 25.98, 24.2, 21.0; IR (CH_2Cl_2, cm^{-1}): 2929, 2854, 1730, 1632, 1447, 1371, 1243, 1020, 966, 751; MS *m/z* (rel intensity): 222 (M^+-60, 24), 157 (84), 140 (72), 125 (100), 95 (48), 81 (56), 67 (42), 55 (68); HRMS Calcd for $C_{16}H_{26}O_4-HOAc$ 222.1620, found: 222.1623.

4.11.4. 4-Acetoxy-2-methylene-4-phenylpentanoic acid methyl ester (27a). 95% Yield, TLC R_f=0.48 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.30 (m, 5H), 6.16 (s, 1H, C=CH_2), 5.39 (s, 1H, C=CH_2), 3.57 (s, 3H, OCH_3), 3.00 (s, 2H, CH_2–C=CH_2), 2.02 (s, 3H, –COCH_3), 1.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.2, 167.7, 143.6, 135.9, 128.6, 127.9, 126.9, 124.7, 83.0, 51.6, 43.7, 24.0, 22.0; IR (CH_2Cl_2, cm^{-1}): 2949, 2845, 1735, 1631, 1496, 1017, 768; MS *m/z* (rel intensity): 261 (M^+−1, 2), 220 (14), 163 (22), 121 (100), 43 (20); HRMS Calcd for $C_{15}H_{18}O_4$ 262.1205, found: 262.1198.

4.11.5. 5-Acetoxy-2-methylene-5-phenylhexanoic acid methyl ester (27b). 96% Yield, TLC R_f=0.52 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.32 (m, 5H), 6.09 (s, 1H, C=CH_2), 5.47 (s, 1H, C=CH_2), 3.69 (s, 3H, OCH_3), 2.14–2.21 (m, 4H), 2.06 (s, 3H, –COCH_3), 1.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 167.2, 144.4, 139.9, 128.0, 126.7, 124.6, 124.3, 83.4, 51.5, 40.8, 26.3, 24.8, 21.9; IR (CH_2Cl_2, cm^{-1}): 2949, 2845, 1731, 1629, 1063, 735; MS *m/z* (rel intensity): 276 (M^+, 5), 187 (13), 121 (100), 77 (12), 43 (62); HRMS Calcd for $C_{16}H_{20}O_4$ 276.1362, found: 276.1362.

4.11.6. 3-(1-Acetoxy-1-cyclohexyl)-2-methylene-propionic acid methyl ester (27c). 96% Yield, TLC R_f=0.47 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.19 (s, 1H, –C=CH_2), 5.50 (s, 1H, –C=CH_2), 3.70 (s, 3H, OCH_3), 2.93 (s, 2H, –CH_2–C=CH_2), 2.11–2.14 (m, 2H), 1.95 (s, 3H, –COCH_3), 1.22–1.47 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 168.0, 136.3, 128.2, 83.1, 51.8, 38.4, 34.3, 31.5, 25.2, 22.5, 22.2, 21.6; IR (CH_2Cl_2, cm^{-1}): 2999, 2933, 2861, 1726, 1627, 1451, 1100; MS *m/z* (rel intensity): 181 (M^+−59, 33), 141 (M^+−99, 33), 99 (64), 98 (75), 81 (25), 43 (100); HRMS Calcd for $C_{13}H_{20}O_4$ 240.1362, found: 240.1367.

4.11.7. 4-(1-Acetoxy-1-cyclohexyl)-2-methylenebutyric acid methyl ester (27d). 90% Yield, TLC R_f=0.47 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.08 (s, 1H, C=CH_2), 5.50 (s, 1H, C=CH_2), 3.70 (s, 3H, OMe), 2.01–2.25 (m, 4H), 1.97–2.01 (m, 2H), 1.96 (s, 3H, –COCH_3), 1.34–1.47 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 167.5, 140.2, 124.7, 83.4, 51.7, 36.0, 34.4, 25.5, 22.1, 21.7; IR (CH_2Cl_2, cm^{-1}): 2935, 2861, 1730, 1632, 1450, 1367, 1107; MS *m/z* (rel intensity): 194 (M^+−60, 20), 135 (40), 134 (51), 99 (100), 95 (47); HRMS Calcd for $C_{13}H_{20}O_4$–CH_3CO_2H 194.1307, found: 194.1301.

4.11.8. *trans*-2-(2-Acetoxy-1-cyclohexyl)acrylic acid methyl ester (35a). 98% Yield, TLC R_f=0.48 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.06 (s, 1H, C=CH_2), 5.45 (s, 1H, C=CH_2), 4.72–4.78 (m, 1H, CHOCO), 3.65 (s, 3H, OCH_3), 2.59–2.65 (m, 1H, CH–C=CH_2), 1.59–2.02 (m, 4H), 1.83 (s, 3H, –COCH_3), 1.17–1.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 167.3, 141.8, 123.9, 74.7, 51.5, 44.2, 32.1, 31.9, 25.3, 24.4, 20.8; IR (CH_2Cl_2, cm^{-1}): 2938, 2860, 1731, 1629, 1438, 925; MS *m/z* (rel intensity): 166 (M^+−60, 73), 151 (47), 134 (45), 79 (48), 43 (100); HRMS Calcd for $C_{12}H_{18}O_4$ 226.1205, found: 226.1196.

4.11.9. *trans*-3-(2-Acetoxy-1-cyclohexyl)-2-methylene-propionic acid methyl ester (35b). 91% Yield, TLC R_f=0.53 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (s, 1H, C=CH_2), 5.53 (s, 1H, C=CH_2), 4.95–4.96 (m, 1H, CHOCO), 3.73 (s, 3H, OCH_3), 2.68–2.69 (m, 1H, CH_2–C=CH_2), 2.31–2.34 (m, 1H, CH_2–C=CH_2), 1.94–2.01 (m, 1H), 1.94 (s, 3H, –COCH_3), 1.63–1.68 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 167.1, 136.9, 126.8, 75.6, 51.8, 43.8, 36.5, 28.9, 28.5, 25.5, 25.3, 20.9; IR (CH_2Cl_2, cm^{-1}): 2952, 2869, 1731, 1632, 1439, 945; MS *m/z* (rel intensity): 240 (M^+, 33), 141 (12), 82 (15), 43 (100), 41 (25).

4.11.10. *cis*-2-(1-Methoxycarbonylvinyl)cyclohexyl benzoate (35c). 94% Yield, TLC R_f=0.62 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99–8.02 (m, 2H), 7.51–7.55 (m, 1H), 7.40–7.44 (m, 1H), 6.17 (s, 1H, C=CH_2), 5.54 (s, 1H, C=CH_2), 5.47 (br s, 1H, CHOCO), 3.75 (s, 3H, OCH_3), 2.88–2.91 (m, 1H, CH–C=CH_2), 1.59–2.07 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 165.6, 141.4, 132.7, 130.9, 129.4, 128.3, 125.2, 70.8, 51.9, 41.5, 30.5, 25.8, 25.3, 20.4; IR (CH_2Cl_2, cm^{-1}): 2936, 2860, 1715, 1629, 1025, 735; MS *m/z* (rel intensity): 288 (M^+, 11), 256 (20), 166 (13), 105 (100), 77 (16); HRMS Calcd for $C_{17}H_{20}O_4$ 288.1362, found: 288.1368.

4.11.11. *cis*-2-(2-Methoxycarbonylallyl)cyclohexyl benzoate (35d). 95% Yield, TLC R_f=0.65 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–8.01 (m, 2H), 7.50–7.52 (m, 1H), 7.39–7.43 (m, 2H), 6.10 (s, 1H, C=CH_2), 5.56 (s, 1H, C=CH_2), 5.26–5.27 (m, 1H, CHOCO), 3.69 (s, 3H, OCH_3), 2.82–2.86 (m, 1H, CH_2–C=CH_2), 2.51–2.57 (m, 1H, CH_2–C=CH_2), 2.18–2.20 (m, 1H), 1.53–1.79 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 166.0, 136.7, 132.6, 130.5, 129.4, 128.2, 127.2, 76.3, 51.8, 43.8, 36.4, 29.0, 28.5, 25.6, 25.4; IR (CH_2Cl_2, cm^{-1}): 2952, 2869, 1714, 1632, 1025; MS *m/z* (rel intensity): 303 (M^++1, 3), 202 (M^+−100, 3), 180 (12), 120 (3), 105 (100), 77 (13); HRMS Calcd for $C_{18}H_{22}O_4$ 302.1518, found: 302.1521.

4.11.12. 2-[2-(Tetrahydropyran-2-yloxy)phenyl]acrylic acid methyl ester (40). 88% Yield, TLC R_f=0.44 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22–7.30 (m, 2H), 7.14–7.16 (m, 1H), 6.99–7.01 (m, 1H), 6.26 (s, 1H, C=CH_2), 5.73 (s, 1H, C=CH_2), 5.43 (br t, 1H), 3.81–3.85 (m, 1H), 3.76 (s, 3H, OCH_3), 3.58–3.61 (m, 1H), 1.55–1.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 154.3, 140.2, 129.9, 129.7, 127.5, 126.1, 121.4, 114.3, 96.2, 61.4, 51.9, 30.2, 25.1, 18.1; IR (CH_2Cl_2, cm^{-1}): 2947, 2874, 1726, 1487, 1455, 1323, 1274, 1233, 1202, 1123, 1035, 962, 920; MS *m/z* (rel intensity): 262 (M^+, 1), 178 (56), 146 (50), 118 (16), 85 (100), 67 (13), 57 (16); HRMS Calcd for $C_{15}H_{18}O_4$ 262.1205, found: 262.1206.

4.11.13. 2-[2-(Tetrahydropyran-2-yloxy)benzyl]acrylic acid methyl ester (47). 82% Yield, TLC R_f=0.71 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.18 (m, 3H), 6.92–6.94 (m, 1H), 6.19 (br s, 1H, C=CH_2), 5.43 (br t, J=3.0 Hz, 1H), 5.35 (br s, 1H, C=CH_2), 3.60–3.84 (m, 2H), 3.76 (s, 3H, OCH_3), 1.60–1.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 155.0, 139.5, 130.6, 127.7, 127.5, 125.6, 121.2, 114.2, 96.1, 61.8,

51.7, 32.2, 30.4, 25.2, 18.7; IR (CH_2Cl_2, cm^{-1}): 2946, 2875, 2844, 1717, 1490, 1455, 1238, 1137, 1037, 968, 754; MS *m/z* (rel intensity): 276 (M^+, 4), 192 (64), 160 (52), 131 (30), 85 (100), 67 (16), 57 (18); HRMS Calcd for $C_{16}H_{20}O_4$ 276.1362, found: 276.1358.

4.11.14. 4-Azido-4-cyclohexyl-2-methylenebutyric acid methyl ester (51c). 62% Yield, TLC R_f=0.73 (hexane/EtOAc=10:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.25 (s, 1H, $-C{=}CH_2$), 5.68 (s, 1H, $-C{=}CH_2$), 3.74 (s, 3H, OCH_3), 3.30 (m, 1H, CHN_3), 2.61–2.63 (m, 1H, $-CH_2-C{=}CH_2$), 2.30–2.33 (m, 1H, $-CH_2-C{=}CH_2$), 1.65–1.76 (m, 6H), 1.11–1.20 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.0, 137.0, 128.0, 66.7, 51.8, 42.4, 34.6, 29.7, 28.2, 26.2, 26.0, 25.9; IR (CH_2Cl_2, cm^{-1}): 2999, 2853, 2103, 1731, 1631, 1450; MS *m/z* (rel intensity): 206 (M^+-31, 33), 100 (31), 83 (42), 55 (100), 41 (98), 39 (43); HRMS Calcd for $C_{12}H_{19}N_3O_2-OCH_3$ 206.1293, found: 206.1294.

4.11.15. 2-(3-Cyclohexyl-3-methoxycarbonylaminopropyl)acrylic acid methyl ester (55d). 82% Yield, TLC R_f=0.82 (hexane/EtOAc=1:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 6.14 (s, 1H, $C{=}CH_2$), 5.58 (s, 1H, $C{=}CH_2$), 4.47 (br d, *J*=9.6 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.49–3.66 (m, 1H), 2.20–2.45 (m, 2H), 1.13–1.75 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 157.4, 140.5, 125.7, 55.8, 52.4, 52.2, 42.7, 31.8, 29.9, 29.3, 28.6, 26.8, 26.62, 26.60; IR (CH_2Cl_2, cm^{-1}): 3326 (N–H), 2926, 2852, 1717, 1634, 1539, 1448, 1244, 1158, 1081, 948; MS *m/z* (rel intensity): 283 (M^+, 4), 200 (100), 170 (16), 168 (48), 136 (12), 124 (30), 88 (16), 55 (12); HRMS Calcd for $C_{15}H_{25}NO_4$ 283.1784, found: 283.1778.

4.12. General procedure of the deprotection of OTHP to the corresponding alcohol catalyzed by ATPB

To a solution of OTHP-protected compound **20a** (143 mg, 0.5 mmol) in a mixture of CH_2Cl_2/MeOH (5 mL, 1:1 by volume) was added ATPB (20 mg, 0.05 mmol) and the solution was stirred at room temperature for 1 h. The solution was concentrated and chromatographed on silica gel column to give the desired **21a** (85 mg, 0.47 mmol) in 93% yield.

4.12.1. 3-Cyclohexyl-3-hydroxy-2-methylenepropionic acid (21a). 93% Yield; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.41 (s, 1H, $C{=}CH_2$), 5.83 (s, 1H, $C{=}CH_2$), 4.11 (d, *J*=7.1 Hz, 1H, $CH-OH$), 1.93–1.97 (m, 1H), 1.56–1.75 (m, 6H), 0.96–1.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 140.3, 128.6, 77.2, 42.3, 29.9, 28.2, 26.3, 26.0, 25.9; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 2927, 1695, 1627, 1450, 1132, 949; MS *m/z* (rel intensity): 166 (M^+-18, 3), 102 (100), 83 (43), 55 (52), 41 (52); HRMS Calcd for $C_{10}H_{16}O_3-H_2O$ 166.0994, found: 166.0996.

4.12.2. 6-Cyclohexyl-6-hydroxy-2-methylenehexanoic acid (21d). 95% Yield; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.25 (s, 1H, $C{=}CH_2$), 5.62 (s, 1H, $C{=}CH_2$), 3.36–3.39 (m, 1H, $CH-OH$), 2.29–2.33 (m, 2H, $CH_2-C{=}CH_2$), 0.99–1.76 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 140.2, 126.5, 76.0, 43.6, 33.4, 31.4, 29.2, 27.8, 26.5, 26.3, 26.2, 24.7; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 2925, 1714, 1627, 1438, 1154, 944; MS *m/z* (rel intensity): 226 (M^+, 8), 165 (100), 139 (3), 105 (13), 77 (11); HRMS Calcd for $C_{13}H_{22}O_3$ 226.1569, found: 226.1575.

4.12.3. 2-(2-Hydroxyphenyl)acrylic acid methyl ester (41).[50] 77% Yield, TLC R_f=0.26 (hexane/EtOAc=5:1); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40 (br s, 1H, OH), 7.12–7.26 (m, 2H), 6.91–6.95 (m, 1H), 6.44 (br s, 1H, $C{=}CH_2$), 5.90 (br s, 1H, $C{=}CH_2$), 3.86 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5, 153.5, 139.4, 130.6, 130.2, 129.8, 124.7, 120.6, 117.3, 52.8; IR (CH_2Cl_2, cm^{-1}): 3393, 2952, 1698, 1622, 1455, 1437, 1326, 1287, 1222, 1112; MS *m/z* (rel intensity): 179 (M^++1, 4), 178 (M^+, 44), 146 (100), 119 (26), 91 (40), 90 (38), 89 (20), 65 (16); HRMS Calcd for $C_{10}H_{10}O_3$ 178.0630, found: 178.0632.

4.13. General procedure to prepare the hydroxy-acid from the corresponding acetoxy-aldehyde

According to general procedure described above, acrolein **26b** (246 mg, 1.0 mmol) was converted to the corresponding acrylic acid **29b**. The crude product of compound **29b** was mixed with K_2CO_3 (207 mg, 1.5 mmol) in 5 mL of MeOH and stirred at room temperature for 6 h. The reaction mixture was concentrated and the crude mixtures were dissolved in ethyl acetate. The organic phase was extracted with water, 1 N HCl and brine, respectively. The organic phase was dried over $MgSO_4$, concentrated and chromatographed on silica gel column to give hydroxy-acid **30b** (172 mg, 0.78 mmol) in 78% yield.

4.13.1. 5-Hydroxy-2-methylene-5-phenylhexanoic acid (30b). 78% Yield, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.45 (m, 5H), 6.22 (s, 1H, $C{=}CH_2$), 5.58 (s, 1H, $C{=}CH_2$), 2.29–2.32 (m, 1H), 2.15–2.18 (m, 1H), 1.96–2.04 (m, 2H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.2, 147.3, 140.1, 128.2, 127.0, 126.7, 124.8, 74.6, 42.8, 30.3, 26.4; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 2923, 1702, 1625, 1446, 1151; MS *m/z* (rel intensity): 220 (M^+, 1), 187 (16), 121 (100), 105 (14), 77 (10); HRMS Calcd for $C_{13}H_{16}O_3$ 220.1099, found: 220.1092.

4.13.2. 4-(1-Hydroxy-1-cyclohexyl)-2-methylenebutyric acid (30d). 82% Yield, ^1H NMR ($CDCl_3$, 400 MHz) δ 6.24 (s, 1H, $C{=}CH_2$), 5.65 (s, 1H, $C{=}CH_2$), 2.37–2.41 (m, 2H, $CH_2-C{=}CH_2$), 1.10–1.65 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.9, 140.7, 126.6, 71.6, 40.9, 37.3, 25.8, 25.3, 22.2; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 2925, 1715, 1627, 1438, 1154; MS *m/z* (rel intensity): 198 (M^+, 2), 137 (70), 99 (100), 81 (38), 55 (22); HRMS Calcd for $C_{11}H_{18}O_3$ 198.1256, found: 198.1259.

4.14. General procedure to prepare the lactone from the acetoxy-acrylate under acidic condition

To a mixture of acetoxy-acrylate **16b** (150 mg, 0.59 mmol) in 3 mL of MeOH was added catalytic amount of acetyl chloride and stirred at room temperature for 7 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the lactone **17b** (91 mg, 0.51 mmol) in 86% yield.

4.14.1. 5-Cyclohexyl-3-methylenedihydrofuran-2-one (17b).[51] 86% Yield; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.18

(br t, J=2.8 Hz, 1H, C═CH_2), 5.59 (br t, J=2.8 Hz, 1H, C═CH_2), 4.21–4.27 (m, 1H, CHOCO), 2.91–2.97 (m, 1H, CH_2–C═CH$_2$), 2.67–2.69 (m, 1H, CH_2–C═CH$_2$), 1.01–1.92 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.4, 134.9, 121.5, 81.4, 43.0, 31.2, 28.1, 27.7, 26.2, 25.6, 25.4; IR (CH_2Cl_2, cm^{-1}): 2927, 2854, 1763, 1450, 1121, 1027; MS m/z (rel intensity): 180 (M$^+$, 10), 151 (44), 134 (72), 97 (100), 69 (80); HRMS Calcd for $C_{11}H_{16}O_2$ 180.1150, found: 180.1158.

4.14.2. 6-Cyclohexyl-3-methylenetetrahydropyran-2-one (17c). 79% Yield, TLC R_f=0.48 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.39 (s, 1H, C═CH_2), 5.53 (s, 1H, C═CH_2), 4.07–4.11 (m, 1H, CHOCO), 2.67–2.68 (m, 1H, CH_2–C═CH$_2$), 2.52–2.53 (m, 1H, CH_2–C═CH$_2$), 1.66–1.93 (m, 9H), 1.13–1.23 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.0, 134.2, 127.5, 84.9, 42.2, 28.1, 27.3, 26.3, 26.0, 25.9, 25.2; IR (CH_2Cl_2, cm^{-1}): 2926, 2854, 1714, 1624, 1174, 1087, 974; MS m/z (rel intensity): 194 (M$^+$, 5), 112 (75), 110 (100), 83 (76), 41 (84); HRMS Calcd for $C_{12}H_{18}O_2$ 194.1307, found: 194.1304.

4.14.3. 5-Methyl-3-methylene-5-phenyldihydrofuran-2-one (28a).[52] 75% Yield, TLC R_f=0.43 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.38 (m, 5H), 6.26 (br s, 1H, C═CH_2), 5.63 (br s, 1H, C═CH_2), 3.15–3.16 (m, 2H, CH_2–C═CH$_2$), 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.6, 144.6, 135.1, 128.6, 127.7, 124.1, 122.5, 83.8, 42.6, 30.0; IR (CH_2Cl_2, cm^{-1}): 2928, 1761, 1667, 1447, 1115, 737; MS m/z (rel intensity): 188 (M$^+$, 22), 173 (100), 105 (76), 77 (41), 68 (68); HRMS Calcd for $C_{12}H_{12}O_2$ 188.0837, found: 188.0828.

4.14.4. 3-Methylene-1-oxa-spiro[4.5]decan-2-one (28c).[53] 79% Yield, TLC R_f=0.40 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.21 (t, J=2.8 Hz, 1H, C═CH_2), 5.59 (t, J=2.8 Hz, 1H, C═CH_2), 2.70 (t, J=2.8 Hz, 2H, CH_2–C═CH$_2$), 1.39–1.80 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 135.6, 122.1, 83.4, 39.5, 37.4, 24.7, 22.4; IR (CH_2Cl_2, cm^{-1}): 2998, 2933, 2859, 1759, 1665, 1448, 1191; MS m/z (rel intensity): 166 (M$^+$, 33), 124 (15), 123 (100), 110 (52), 68 (40); HRMS Calcd for $C_{10}H_{14}O_2$ 166.0994, found: 166.0993.

4.14.5. *trans*-3-Methylenehexahydrobenzofuran-2-one (36a).[54] 89% Yield, TLC R_f=0.43 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.04 (d, J=3.2 Hz, 1H, C═CH_2), 5.36 (d, J=3.2 Hz, 1H, C═CH_2), 3.67–3.72 (m, 1H, CHOCO), 1.24–2.39 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 139.6, 117.0, 83.0, 48.8, 30.4, 25.7, 24.8, 24.0; IR (CH_2Cl_2, cm^{-1}): 2939, 2864, 1769, 1675, 1456, 1117, 935; MS m/z (rel intensity): 152 (M$^+$, 2), 124 (100), 95 (83), 79 (81), 67 (51); HRMS Calcd for $C_9H_{12}O_2$ 152.0837, found: 152.0843.

4.14.6. *trans*-3-Methyleneoctahydrochromen-2-one (36b).[54] 87% Yield, TLC R_f=0.45 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.35 (s, 1H, C═CH_2), 5.50 (s, 1H, C═CH_2), 4.07–4.13 (m, 1H, CHOCO), 2.64–2.65 (m, 1H, CH_2–C═CH$_2$), 2.51–2.52 (m, 1H, CH_2–C═CH$_2$), 1.25–2.04 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 134.6, 127.9, 84.8, 45.1, 29.1, 28.9, 27.7, 25.8, 25.7; IR (CH_2Cl_2, cm^{-1}): 2951, 2869, 1759, 1666, 1436, 1125, 941; MS m/z (rel intensity): 166 (M$^+$, 7), 97 (100), 96 (43), 40 (70), 39 (92); HRMS Calcd for $C_{10}H_{14}O_2$ 166.0994, found: 166.1003.

4.14.7. 3-Methylenechroman-2-one (48).[55] 67% Yield, TLC R_f=0.64 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.06–7.28 (m, 4H), 6.43 (s, 1H, –C═CH_2), 5.78 (s, 1H, –C═CH_2) 3.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.2, 150.9, 131.8, 128.4, 128.2, 127.7, 124.5, 121.2, 117.0, 32.0; IR (CH_2Cl_2, cm^{-1}): 2927, 2855, 1713, 1456, 1224, 1150; MS m/z (rel intensity): 160 (M$^+$, 100), 131 (48), 105 (8), 91 (8), 77 (16), 69 (18); HRMS Calcd for $C_{10}H_8O_2$ 160.0524, found: 160.0521.

4.15. General procedure to prepare the lactone from benzoxy-acrylates promoted by NaOMe/MeOH

To a mixture of benzoate-acrylate **35c** (150 mg, 0.52 mmol) in 4 mL of MeOH was added NaOMe (31 mg, 0.57 mmol) and stirred at room temperature for 4 h. The reaction mixture was concentrated and chromatographed on silica gel column to give the lactone **36c** (60 mg, 0.40 mmol) in 76% yield.

4.15.1. *cis*-3-Methylenehexahydrobenzofuran-2-one (36c).[54] 76% Yield, TLC R_f=0.41 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.19 (d, J=2.4 Hz, 1H, C═CH_2), 5.50 (d, J=2.4 Hz, 1H, C═CH_2), 4.51–4.56 (m, 1H, CHOCO), 3.00–3.03 (m, 1H, CH–C═CH$_2$), 1.25–1.87 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 139.9, 119.7, 76.9, 39.6, 28.9, 26.3, 21.1, 20.5; IR (CH_2Cl_2, cm^{-1}): 2938, 1771, 1224, 1131, 935.

4.15.2. *cis*-3-Methyleneoctahydrochromen-2-one (36d).[54] 70% Yield, TLC R_f=0.40 (hexane/EtOAc=3:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.21 (t, J=2.8 Hz, 1H, C═CH_2), 5.60 (t, J=2.8 Hz, 1H, C═CH_2), 4.35–4.38 (m, 1H, CHOCO), 2.99–3.05 (m, 1H, CH–C═CH$_2$), 2.64–2.65 (m, 1H, CH–C═CH$_2$), 1.27–2.08 (m, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 135.0, 121.7, 81.1, 45.1, 32.5, 28.6, 27.9, 25.4, 25.3; IR (CH_2Cl_2, cm^{-1}): 2942, 2868, 1719, 1622, 1186, 944; MS m/z (rel intensity): 166 (M$^+$, 6), 137 (10), 98 (12), 97 (100), 69 (24); HRMS Calcd for $C_{10}H_{14}O_2$ 166.0994, found: 166.0986.

4.15.3. General procedure to prepare lactone from the hydroxy-acid promoted by *o*-nitrobenzenesulfonyl chloride. Anhydrous Na_2CO_3 (456.0 mg, 4.34 mmol) was added to a solution of **21a** (79.2 mg, 0.43 mmol) in CH_2Cl_2 (2.5 mL). After 15 min, *o*-nitrobenzenesulfonyl chloride (144.1 mg, 0.65 mmol) was added and the mixture left to stir at room temperature for 2 h. The mixture was diluted with CH_2Cl_2 (7.5 mL) and water (2.5 mL) and stirred for 15 min. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Purification by silica gel column chromatography (hexane/EtOAc=98:2) provided **17a** as a colorless oil (58.3 mg, 81%).

4.15.4. 4-Cyclohexyl-3-methylene-1-oxetan-2-one (17a). 81% Yield, TLC R_f=0.42 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.91 (t, J=1.7 Hz, 1H, C═CH_2), 5.42

(t, J=1.7 Hz, 1H, C=CH_2), 4.69 (dt, J=7.1, 1.7 Hz, 1H, CHOCO), 1.10–1.87 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.7, 145.2, 115.1, 83.2, 40.9, 28.0, 27.4, 26.0, 25.4, 25.3; IR (CH_2Cl_2, cm^{-1}): 2928, 2854, 1827, 1452, 1206, 939; MS m/z (rel intensity): 149 (M^+-17, 20), 111 (51), 83 (70), 55 (96), 43 (100); HRMS Calcd for $C_{10}H_{14}O_2$ 166.0994, found: 166.0990.

4.15.5. 7-Cyclohexyl-3-methyleneoxepan-2-one (17d). 87% Yield, TLC R_f=0.47 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.64 (s, 1H, C=CH_2), 5.36 (s, 1H, C=CH_2), 3.90–3.95 (m, 1H, CHOCO), 2.32–2.44 (m, 2H, CH_2–C=CH_2), 1.04–1.84 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 143.5, 122.2, 84.1, 42.9, 31.4, 30.6, 28.6, 27.9, 26.3, 26.1, 26.0, 25.9; IR (CH_2Cl_2, cm^{-1}): 2926, 2854, 1729, 1449, 1168, 928, 878; MS m/z (rel intensity): 208 (M^+, 2), 180 (20), 125 (73), 97 (100), 83 (57); HRMS Calcd for $C_{13}H_{20}O_2$ 208.1463, found: 208.1472.

4.15.6. 6-Methyl-3-methylene-6-phenyltetrahydropyran-2-one (28b). 71% Yield, TLC R_f=0.45 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.36 (m, 5H), 6.45 (s, 1H, C=CH_2), 5.48 (s, 1H, C=CH_2), 2.53–2.57 (m, 1H), 2.32–2.38 (m, 2H), 2.12–2.17 (m, 1H), 1.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 143.9, 132.9, 128.7, 128.4, 127.3, 124.4, 84.9, 34.2, 30.9, 24.5; IR (CH_2Cl_2, cm^{-1}): 2979, 2932, 1714, 1622, 1446, 1140, 929; MS m/z (rel intensity): 202 (M^+, 9), 187 (9), 121 (100), 105 (11), 43 (64); HRMS Calcd for $C_{13}H_{14}O_2$ 202.0994, found: 202.0997.

4.15.7. 2-Methylene-1-oxaspiro[5.5]undecan-2-one (28d). 80% Yield, TLC R_f=0.35 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.44 (s, 1H, C=CH_2), 5.54 (s, 1H, C=CH_2), 2.62–2.66 (m, 2H, CH_2–C=CH_2), 1.73–1.86 (m, 6H), 1.32–1.58 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6, 133.4, 127.7, 82.2, 36.5, 31.9, 25.2, 23.5, 21.5; IR (CH_2Cl_2, cm^{-1}): 2929, 2861, 1714, 1622, 1447, 1132; MS m/z (rel intensity): 180 (M^+, 64), 137 (100), 124 (46), 82 (22), 55 (24); HRMS Calcd for $C_{11}H_{16}O_2$ 180.1150, found: 180.1151.

4.15.8. 3-Methylene-3*H*-benzofuran-2-one (42).[37] A solution of hydroxy-ester **41** (49.9 mg, 0.28 mmol) in dry toluene (1.4 mL) was treated with trifluoroacetic acid (5 drops). The lactone **42** was formed after the mixture was refluxed for 2 h. The lactone **42** was known to be stable for a few days in solution. However, it polymerizes quickly on the silica gel during the separation. Therefore, the reaction mixture was cooled down to room temperature and then added cyclopentadiene (0.2 mL, 2.8 mmol) and stirred at ambient temperature for 1.5 h. The resulting solution was concentrated under vacuum and two diastereomers (55% yield) can be separated by column chromatography.

Compound **43**-minor: pale yellow solid, mp 51–52 °C; 11% yield, TLC R_f=0.82 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.32 (m, 2H), 7.09–7.15 (m, 2H), 6.50–6.52 (m, 1H), 6.18–6.20 (m, 1H), 3.22 (s, 1H, bridgehead-H), 2.91 (s, 1H, bridgehead-H), 2.11–2.15 (m, 1H), 2.04–2.06 (m, 1H), 1.82–1.86 (m, 1H), 1.62–1.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.4, 152.8, 139.6, 133.2, 133.1, 128.4, 123.9, 123.1, 110.5, 55.6, 50.9, 48.0, 43.4, 41.8; IR (CH_2Cl_2, cm^{-1}): 3063, 2973, 2877, 1794, 1617, 1475, 1460, 1234, 1125, 1073, 1037; MS m/z (rel intensity): 212 (M^+, 56), 146 (88), 118 (68), 90 (58), 66 (100); HRMS Calcd for $C_{14}H_{12}O_2$ 212.0837, found: 212.0834.

43-major: pale yellow solid, mp 83–84 °C; 44% yield, TLC R_f=0.87 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22–7.27 (m, 1H), 7.01–7.09 (m, 3H), 6.61–6.64 (m, 1H), 6.19–6.21 (m, 1H), 3.19 (s, 1H, bridgehead-H), 3.07 (s, 1H, bridgehead-H), 2.44–2.49 (m, 2H), 1.50–1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.2, 153.1, 141.0, 134.0, 132.0, 128.3, 124.6, 123.5, 110.2, 54.4, 50.6, 47.2, 43.6, 42.4; IR (CH_2Cl_2, cm^{-1}): 3053, 2974, 2875, 1795, 1615, 1478, 1461, 1236, 1123, 1075, 1038; MS m/z (rel intensity): 212 (M^+, 40), 146 (76), 118 (48), 90 (26), 66 (100); HRMS Calcd for $C_{14}H_{12}O_2$ 212.0837, found:. 212.0838.

4.15.9. 5-Cyclohexyl-3-methylenepyrrolidin-2-one (52c).[39] The solution of the azide **51c** (30.8 mg, 0.13 mmol) and Ph_3P (39.3 mg, 0.15 mmol) in THF (1 mL) was stirred at room temperature for 30 min. To the resulting solution was added H_2O (0.1 mL) and stirred at room temperature for 6 h. The reaction mixture was concentrated, chromatographed on silica gel column to give the lactam **52c** (18.6 mg, 0.10 mmol) in 80% yield. TLC R_f=0.5 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (br, 1H, NH), 5.94 (t, J=2.7 Hz, 1H, CH=CH_2), 5.30 (s, 1H, CH=CH_2), 3.38–3.40 (m, 1H, CHNCO), 2.83–2.85 (m, 1H, CH_2CH=CH_2), 2.51–2.56 (m, 1H, –CH_2CH=CH_2), 0.90–1.77 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 139.6, 115.4, 56.2, 43.6, 30.9, 28.7, 28.5, 26.3, 25.8, 25.7, 25.8; IR (CH_2Cl_2, cm^{-1}): 3216 (NH), 2928, 2855, 1697, 1661, 1450, 1264, 928; MS m/z (rel intensity) 178 (M^+-1, 2), 96 (100), 55 (7), 53 (15), 41 (20); HRMS Calcd for $C_{11}H_{17}NO$ 179.1310, found: 179.1313.

4.15.10. 6-Cyclohexyl-3-methylene-2-oxo-piperidine-1-carboxylic acid methyl ester (56d). A mixture of the acrylate **55d** (101.9 mg, 0.36 mmol) in toluene (3.2 mL) was added Me_3Al (2.0 M in toluene, 0.35 mL, 0.71 mmol) at 0 °C dropwise over 5 min and stirred at 0 °C for 2 h. The reaction mixture was quenched by the addition of brine at 0 °C. The aqueous phase was separated and extracted with ethyl acetate. The organic extracts were combined, dried, concentrated and chromatographed on silica gel column to give compound **56d** (65 mg, 0.26 mmol) in 72% yield. TLC R_f=0.64 (hexane/EtOAc=1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.11 (s, 1H, C=CH_2), 4.77 (s, 1H, C=CH_2), 3.66 (s, 3H, –OCH_3), 3.52–3.55 (m, 1H), 2.13–2.17 (m, 2H), 1.14–1.76 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3, 157.7, 155.9, 107.5, 55.9, 52.4, 42.9, 30.0, 29.7, 29.6, 28.6, 26.8, 26.64, 26.63; IR (CH_2Cl_2, cm^{-1}): 2927, 2852, 1703, 1634, 1539, 1449, 1361, 1258, 1191, 1148, 1081, 962, 893; MS m/z (rel intensity): 252 (M^++1, 2), 251 (M^+, 1), 200 (28), 182 (40), 170 (56), 107 (100), 88 (48), 76 (48); HRMS Calcd for $C_{14}H_{21}NO_3$ 251.1521, found: 251.1531.

4.16. General procedure to prepare the α-keto ester from the methyl acrylate by ozonolysis

In a 25 mL of two-necked flask, equipped with a magnetic

stirrer, a drying tube and a gas dispersing tube (with porous fritted tip), were placed 10 mL of CH_2Cl_2 and α-substituted acrylate **8a** (250.7 mg, 1.36 mmol). A stream of ozone was bubbled through the solution at −78 °C. Ozone treatment was terminated when the mixture assumed a blue color. A stream of nitrogen removed excess ozone. To the resulted solution was added Ph_3P (356.7 mg, 1.36 mmol) and the reaction was warmed slowly to room temperature and stirred for 4 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give 176 mg of α-keto ester **9a** in 69% yield.

4.16.1. 2-Oxononanoic acid methyl ester (9a). 69% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3H, OCH_3), 2.83 (t, *J*=7.1 Hz, 2H, $-CH_2(C{=}O)$), 1.61–1.66 (m, 2H), 1.20–1.35 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.3, 161.6, 52.8, 39.3, 31.5, 28.8, 22.9, 22.5, 14.0; IR (CH_2Cl_2, cm^{-1}): 1728 (C=O), 1435, 1273, 1067; MS *m/z* (rel intensity): 186 (M^+, 3), 128 (12), 127 (100), 109 (10), 97 (3); HRMS Calcd for $C_{10}H_{18}O_3$ 186.1256, found 186.1255.

4.16.2. 2-Oxo-2-(3-oxocyclohexyl)acetic acid methyl ester (9b). 64% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3H, OCH_3), 2.00–2.60 (m, 6H), 1.50–1.85 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.4, 193.9, 161.1, 53.1, 46.1, 41.2, 40.8, 26.6, 24.5; IR (CH_2Cl_2, cm^{-1}): 1732, 1706 (C=O), 1446, 1251, 1106, 1061, 1033; MS *m/z* (rel intensity): 184 (M^+, 8), 156 (6), 125 (50), 97 (100), 69 (76), 55 (38), 41 (88).

4.16.3. 3,3-Dimethyl-2,5-dioxohexanoic acid (9c). 71% Yield; yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H, OCH_3), 3.12 (s, 2H, $-CH_2C{=}O$), 2.13 (s, 3H, CH_3CO), 1.26 (s, 6H, $C(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.4, 196.9, 161.9, 54.0, 52.3, 43.7, 29.9, 24.8; IR (CH_2Cl_2, cm^{-1}): 2500–3550 (OH), 1689 (C=O), 1622, 1416, 1284, 1152; MS *m/z* (rel intensity): 187 (M^++1, 2), 127 (42), 99 (22), 83 (3), 69 (3), 59 (4), 43 (100).

4.16.4. 10-Hydroxy-2-oxodecanoic acid methyl ester (9d). 62% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3H, OCH_3), 3.62 (t, *J*=6.6 Hz, 2H, $-CH_2OH$), 2.83 (t, *J*=7.3 Hz, 2H, $-CH_2(C{=}CH_2)-$), 1.25–1.70 (m, 13H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.3, 161.6, 62.8, 52.8, 39.2, 32.6, 29.1, 28.8, 25.6, 22.8; IR (CH_2Cl_2, cm^{-1}): 3441 (OH), 1735 (C=O), 1436, 1263, 1067; MS *m/z* (rel intensity): 216 (M^+, 2), 157 (32), 139 (35), 121 (17), 97 (23), 81 (13), 69 (100), 55 (82), 41 (39); HRMS Calcd for $C_{11}H_{20}O_4$ 216.1362, found 216.1356.

4.16.5. 10-Acetoxy-2-oxodecanoic acid methyl ester (9e). 69% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.05 (t, *J*=6.9 Hz, 2H, CH_2OAc), 3.86 (s, 3H, OCH_3), 2.83 (t, *J*=7.3 Hz, 2H, $CH_2(C{=}CH_2)-$), 2.04 (s, 3H, $OCOCH_3$), 1.25–1.65 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.3, 171.2, 161.6, 64.5, 52.8, 39.2, 29.1, 29.0, 28.8, 28.5, 25.8, 22.9, 21.0; IR (CH_2Cl_2, cm^{-1}): 1731 (C=O), 1437, 1237, 1064; MS *m/z* (rel intensity): 258 (M^+, 1), 199 (42), 157 (92), 139 (52), 95 (12), 69 (100), 55 (70), 43 (88); HRMS Calcd for $C_{13}H_{22}O_5$ 258.1467, found 258.1461.

4.16.6. 10-Iodo-2-oxodecanoic acid methyl ester (9f). 67% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3H, OCH_3), 3.18 (t, *J*=6.8 Hz, 2H, $-CH_2I$), 2.83 (t, *J*=7.2 Hz, 2H, $-CH_2C{=}O$), 1.82 (quin, *J*=7.1 Hz, 2H), 1.52–1.65 (m, 2H), 1.31–1.40 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.2, 161.6, 52.8, 39.2, 33.4, 30.3, 29.0, 28.8, 28.2, 22.8, 7.03; IR (CH_2Cl_2, cm^{-1}): 1725 (C=O), 1433, 1268, 1061; MS *m/z* (rel intensity): 326 (M^+, 2), 267 (100), 197 (8), 181 (10), 169 (11), 155 (13), 139 (16), 91 (30), 69 (58), 55 (60), 41 (39); HRMS Calcd for $C_{11}H_{19}IO_3$ 326.0379, found 326.0374.

4.16.7. 2-Oxononanamide (11g). 90% Yield; white solid, mp 91–92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.85 (br s, 1H, NH_2), 5.80 (br s, 1H, NH_2), 2.90 (t, *J*=9.7 Hz, 2H, $-CH_2(C{=}O)$), 1.55–1.65 (m, 2H), 1.15–1.45 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.8, 162.1, 36.5, 31.6, 29.0, 23.2, 22.6, 14.0; IR (CH_2Cl_2, cm^{-1}): 3404 (N–H), 3216 (N–H), 1716 (C=O), 1671 ($CONH_2$), 1403, 1103; MS *m/z* (rel intensity): 171 (M^+, 3), 149 (8), 127 (31), 109 (5), 62 (46), 57 (50), 45 (100); HRMS Calcd for $C_9H_{17}NO_2$ 171.1259, found 171.1266.

4.16.8. 1-Pyrrolidin-1-yl-nonane-1,2-dione (11h). 85% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.60 (t, *J*=6.5 Hz, 2H, NCH_2), 3.51 (t, *J*=6.8 Hz, 2H, NCH_2), 2.83 (t, *J*=7.4 Hz, 2H, $-CH_2C{=}O$), 1.77–1.96 (m, 4H), 1.56–1.63 (m, 2H), 1.25–1.40 (m, 8H), 0.88 (t, *J*=6.8 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.1, 163.2, 47.2, 46.2, 39.2, 31.6, 29.1, 29.0, 26.3, 23.6, 23.0, 22.5, 14.0; IR (CH_2Cl_2, cm^{-1}): 1711 (C=O), 1634 (C=O), 1400, 1086; MS *m/z* (rel intensity): 225 (M^+, 8), 98 (88), 75 (100).

4.16.9. *N*-(2-Oxononanoyl)valine methyl ester (11i). 85% Yield; pale yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (br d, *J*=8.6 Hz, 1H, NH), 4.48 (d, *J*=9.4 Hz, 0.5H), 4.47 (d, *J*=9.4 Hz, 0.5H), 3.75 (s, 3H, OCH_3), 2.90 (t, *J*=7.6 Hz, 2H), 2.22 (sext, *J*=5.2 Hz, 1H), 1.52–1.65 (m, 3H), 1.20–1.35 (m, 7H), 0.85–0.97 (m, 9H, 3xCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.6, 171.3, 160.0, 57.3, 52.3, 36.8, 31.6, 31.3, 29.0, 23.2, 22.6, 18.9, 17.7, 14.0; IR (CH_2Cl_2, cm^{-1}): 3400 (N–H), 1741 (C=O), 1681 (C=O), 1510, 1461, 920; MS *m/z* (rel intensity): 285 (M^+, 8), 254 (2), 224 (9), 158 (15), 130 (100), 98 (15), 72 (22), 57 (42), 41 (20); HRMS Calcd for $C_{15}H_{27}NO_4$ 285.1940, found 285.1947.

4.17. General procedure to prepare the α-keto lactone from α-methylene lactone by ozonolysis in CH_2Cl_2

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar is charged with α-methylene lactone **17b** (90.0 mg, 0.50 mmol) in CH_2Cl_2 (5 mL). The flask is cooled to −78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharged. To the resulted solution was added Ph_3P (104.9 mg, 0.40 mmol) and warmed slowly to room temperature. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give α-keto lactone **17b′** (72.8 mg, 0.40 mmol) in 80% yield.

4.17.1. 5-Cyclohexyl-3-hydroxy-5*H*-furan-2-one (17b′). 80% Yield, TLC R_f=0.4 (hexane/EtOAc=10:1); enol form only; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.21 (d, J=2.0 Hz, 1H, C*H*=COH), 5.87 (br s, 1H, OH), 4.74 (dd, J=5.6 and 2.0 Hz, 1H, C*H*OCO), 1.64–1.80 (m, 5H), 1.14–1.27 (m, 6H,); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3, 142.2, 117.6, 83.7, 41.8, 28.2, 28.1, 26.1, 25.7, 25.6; IR (CH_2Cl_2, cm^{-1}): 3391 (OH), 2928, 1757, 1264, 1037; MS *m/z* (rel intensity): 182 (M^+, 2), 137 (12), 100 (100), 83 (18), 55 (33); HRMS Calcd for $C_{10}H_{14}O_3$ 182.0943, found: 182.0940.

4.17.2. 7-Cyclohexyl-oxepane-2,3-dione (17d′). 80% Yield, TLC R_f=0.43 (hexane/EtOAc=3:1); keto form only; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95–3.99 (m, 1H, C*H*$_2$–CO), 2.60–2.62 (m, 1H), 2.48–2.51 (m, 1H), 1.03–1.99 (m, 15H,); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.1, 166.2, 82.8, 42.4, 38.2, 29.8, 28.5, 28.2, 26.1, 25.8, 25.7, 20.1; IR (CH_2Cl_2, cm^{-1}): 2925, 2854, 1747, 1714, 1652, 1451, 1118, 736; MS *m/z* (rel intensity): 210 (M^+, 33), 122 (40), 109 (100), 81 (78), 67 (86); HRMS Calcd for $C_{12}H_{18}O_3$ 210.1256, found: 210.1266.

4.17.3. 5-Methyl-5-phenyldihydrofuran-2,3-dione (28a′) and 3-Hydroxy-5-methyl-5-phenyl-5*H*-furan-2-one (28a″).[56] 73% Yield, TLC R_f=0.37 (hexane/EtOAc=10:1); a mixture of keto and enol forms (1: 5). Keto form **28a′**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.40 (m, 5H), 3.19–3.20 (m, 1H, C*H*$_2$–CO), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.2, 159.4, 142.7, 129.0, 128.7, 125.1, 83.5, 48.1, 31.9. Enol form (**28a″**): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.40 (m, 5H), 6.52 (s, 1H, C*H*=COH), 1.89 (s, 3H), 1.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.7, 142.7, 140.3, 128.5, 128.3, 124.8, 123.9, 85.7, 22.7; IR (CH_2Cl_2, cm^{-1}): 2500–3500 (OH), 2931, 1746, 1264, 915; MS *m/z* (rel intensity): 190 (30), 189 (52), 144 (100), 134 (83), 104 (41); HRMS Calcd for $C_{11}H_{10}O_3$ 190.0630, found: 190.0627.

4.17.4. 1-Oxaspiro[4.5]decane-2,3-dione (28c′) and 3-hydroxy-1-oxaspiro[4.5]dec-3-en-2-one (28c″).[57] 80% Yield, TLC R_f=0.35 (hexane/EtOAc=10:1), a mixture of keto and enol forms (2: 5). Keto form **28c′**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (s, 2H, C*H*$_2$–CO), 1.26–1.89 (m, 10H,); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.1, 159.9, 83.3, 45.7, 29.6, 24.3, 22.0 (2°). Enol form **28c″**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.31 (s, 1H, C*H*=COH), 1.26–1.89 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.9, 141.3, 124.1, 85.4, 35.8, 24.7, 22.6; IR (CH_2Cl_2, cm^{-1}): 3433 (OH), 2932, 1742, 1264, 1193, 972; MS *m/z* (rel intensity): 168 (M^+, 30), 123 (100), 122 (32), 112 (47), 67 (24); HRMS Calcd for $C_9H_{12}O_3$ 168.0786, found: 168.0784.

4.17.5. 3-Hydroxy-5,6,7,7a-tetrahydro-4*H*-benzofuran-2-one (36c″). 81% Yield, TLC R_f=0.37 (hexane/EtOAc=3:1); enol form only; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.60 (dd, J=11.2, 6.0 Hz, 1H, C*H*OCO), 2.93–2.98 (m, 1H), 2.40–2.53 (m, 1H), 1.88–2.03 (m, 3H), 1.21–1.38 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.9, 134.9, 134.0, 78.4, 33.9, 25.4, 23.7, 22.7; IR (CH_2Cl_2, cm^{-1}): 3253 (OH), 2939, 1752, 1218, 1061; MS *m/z* (rel intensity): 154 (M^+, 22), 109 (100), 97 (22), 81 (20), 69 (20); HRMS Calcd for $C_8H_{10}O_3$ 154.0630, found: 154.0635.

4.18. General procedure to prepare the α-keto lactone from α-methylene lactone by ozonolysis in methanol/CH_2Cl_2

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube and a magnetic stirring bar is charged with α-methylene-lactone **17c** (95 mg, 0.49 mmol) in CH_2Cl_2 (3 mL) and methanol (2 mL). The flask is cooled to −78 °C and ozone is bubbled through the solution. When the solution turns blue, ozone addition is stopped. Nitrogen is passed through the solution until the blue color is discharges. To the resulted solution was added Ph_3P (131 mg, 0.50 mmol) and warmed slowly to room temperature. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give α-keto lactone **17c′** (79.3 mg, 0.35 mmol) in 71% yield.

4.18.1. 5-Cyclohexyl-2-hydroxytetrahydrofuran-2-carboxylic acid methyl ester (17c″). 71% Yield; a mixture of two diastereomers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.83–3.88 (m, 1H), 3.82 (s, 3H), 0.99–1.26 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.8, 171.7, 102.0, 101.5, 87.1, 85.1, 52.9, 43.4, 42.2, 35.5, 35.2, 29.9, 29.4, 28.7, 28.5, 27.9, 26.4, 25.9, 25.8, 25.7; IR (CH_2Cl_2, cm^{-1}): 3447 (OH), 2924, 2852, 1747, 1449, 1272, 1198, 1156, 1056, 890; MS *m/z* (rel intensity): 227 (M^+-1, 2), 151 (95), 145 (68), 133 (42), 127 (45), 109 (45), 85 (100), 67 (43), 55 (46); HRMS Calcd for $C_{12}H_{20}O_4-CO_2CH_3$ 169.1229, found: 169.1233.

4.18.2. 2-Hydroxy-5-methyl-5-phenyltetrahydrofuran-2-carboxylic acid methyl ester (28b″). 75% Yield; a mixture of two diastereomers; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23–7.49 (m, 5H), 3.99 (br s, 1H, OH), 3.87 and 3.83 (s, 3H), 2.14–2.58 (m, 4H), 1.72 and 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5, 172.6, 147.5, 147.0, 128.1, 128.0, 126.7, 126.6, 124.9, 124.6, 102.4, 88.0, 87.8, 53.2, 53.0, 39.2, 38.9, 35.1, 34.9, 30.9, 29.2; IR (CH_2Cl_2, cm^{-1}): 3472 (OH), 2924, 2852, 1744, 1494, 1445, 1265, 1066, 892; MS *m/z* (rel intensity): 221 (M^+-15, 60), 177 (100), 161 (60), 131 (64), 117 (44), 105 (42), 91 (28), 77 (25); HRMS Calcd for $C_{13}H_{16}O_4-CH_3$ 221.0814, found: 221.0810.

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An efficient route to 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones as potential nAChRs ligands

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Abstract—A new efficient pathway to synthesise 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones is described. This reaction sequence involved, as a key step, a Suzuki cross-coupling reaction between various boronic acids and an 6-iodo-2,3-dihydropyridin-4-one. A final deprotecting step furnished the attempted products.

1. Introduction

Recently, numerous studies have focused on the synthesis of ligands for neuronal nicotinic acetylcholine receptors (nAChRs).[1,2] Because, structures analogues of well established nAChRs ligands have been suggested as potential therapeutic agents for several neurological disorders, including attention deficit, hyperactivity disorder, Tourette's syndrome, schizophrenia, Alzheimer's and Parkinson's diseases.[3]

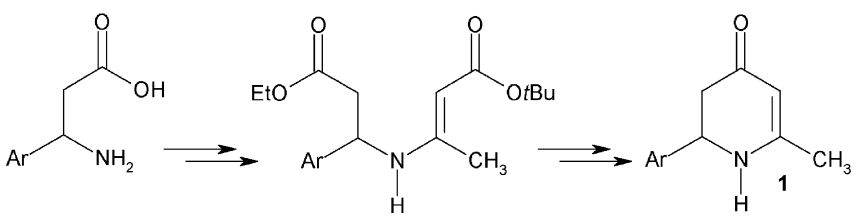
Moreover, most of the nAChRs ligands with high affinity contain pyridine and cyclic amine pharmacophoric moieties, and comprehensive reviews, which summarized the structure–activity relationships of ligands for nAChRs, have emphasized the importance in the ligand structure of a π-system, such as a heteroaromatic ring or carbonyl group as a hydrogen bond acceptor moiety, and a basic cyclic amine group.[4]

Dihydropyridinones are interesting building blocks for a large variety of heterocycles because their aminoenone moiety can be used in various reactions leading to key intermediates particularly useful in the synthesis of alkaloids and pharmacologically active agents.[5] In peculiar, we have pointed out the interest of the dihydropyridinones of type **1** (Scheme 1) as memory enhancers in relation to their nicotinic acetylcholine receptor activity.[6] Recently, we have developed a new versatile and efficient four steps procedure for the preparation of 6-alkyl-2-(het)aryl-2,3-dihydro-1*H*-pyridin-4-ones **1**,[7] starting from available β-(het)aryl-β-amino acids[8] (Scheme 1).

With the aim to determine the influence of the double bond position on the pharmacological properties we have turned our attention to synthesise the isomers compounds 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones **2**.[9]

2. Results and discussion

In connection with our previous works, we have studied the



Scheme 1.

Keywords: Cross-coupling; Suzuki reaction; Boronic acids; Heterocycles; Dihydropyridinone.
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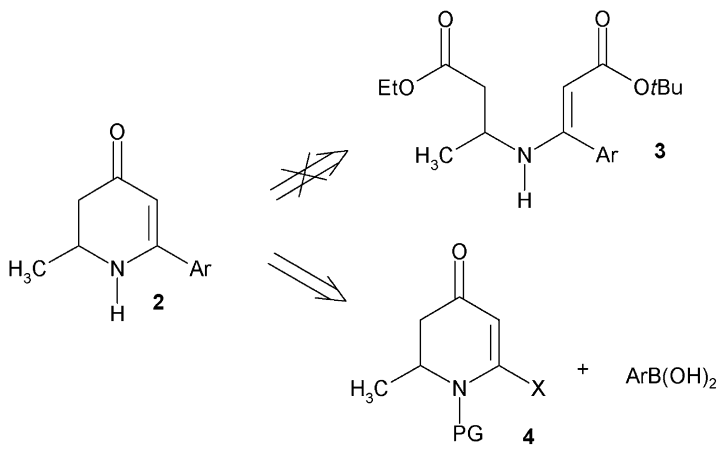
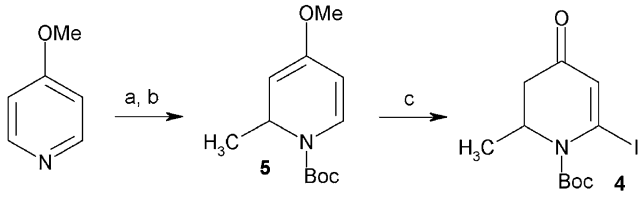


Scheme 2. Retrosynthetic approach.

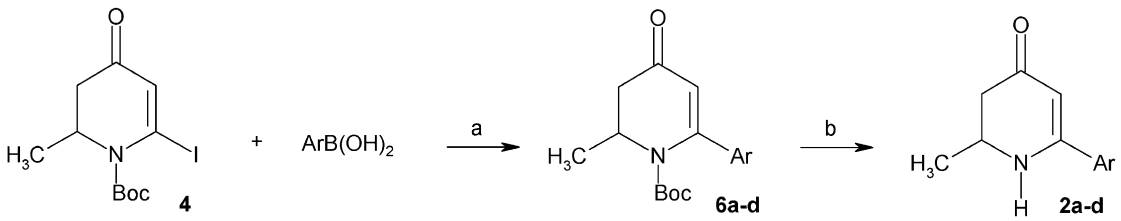


Scheme 3. Reagents and conditions: (a) (i) PhOCOCl (1.01 equiv.), THF, −25 °C; (ii) MeMgBr (1.05 equiv.), THF, −25 °C to room temperature; (b) *t*-BuOK (4 equiv.), THF, −60 °C (91% in 2 steps); (c) (i) *n*-BuLi (1.2 equiv.), THF, −60 °C; (ii) I_2 (1.1 equiv.), THF, −60 °C to room temperature; (iii) HCl 1 N (76%).

enaminone formation by the use of the acetate salt of ethyl 3-aminobutyrate and *tert*-butyl β-aryl-β-ketoester but this method failed to produce the expected enaminone intermediate **3** and instead led to degradation products (Scheme 2).

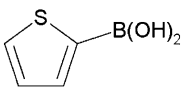
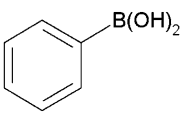
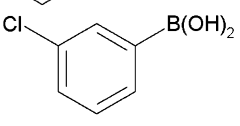
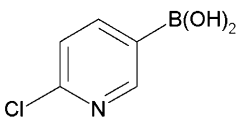
We have therefore envisaged a second synthetic procedure which consisted in a Suzuki cross-coupling reaction between a protected 6-halo-2,3-dihydroprydin-4-one **4** and various boronic acids (Scheme 2).

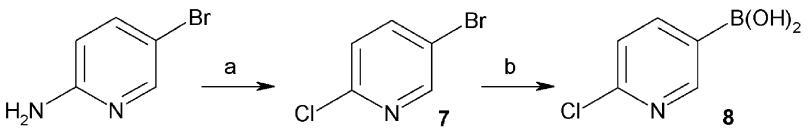
As illustrated in Scheme 3, the intermediate **4** was prepared by applying Comins's methodology.[10] 1-Acylpyridinium



Scheme 4. Reagents and conditions: (a) $NaHCO_3$ (2.5 equiv.), 5 mol% $Pd(PPh_3)_4$, DME/H_2O (v/v), reflux; (b) TFA (10 equiv.), CH_2Cl_2, room temperature.

Table 1. Suzuki cross-coupling reaction of 6-iodo-2,3-dihydropyridin-4-one with arylboronic acids and clivage of Boc protecting group in acidic conditions

Entry	$ArB(OH)_2$	Cross-coupled product (isolated yield)	Deprotected product (isolated yield)
1		**6a** (87%)	**2a** (91%)
2		**6b** (78%)	**2b** (92%)
3		**6c** (78%)	**2c** (91%)
4		**6d** (80%)	**2d** (76%)



Scheme 5. Reagents and conditions: (a) (i) $NaNO_2$ (2 equiv.), HCl 6 N, 0 °C; (ii) CuCl (1.25 equiv.), 0 °C to room temperature (56%); (b) (i) *n*-BuLi (1.2 equiv.), Et_2O, −78 °C; (ii) $B(OiPr)_3$ (1.2 equiv.), Et_2O, −78 °C to room temperature (78%).

salt was formed in situ by addition of phenyl chloroformate to 4-methoxypyridine in THF at −25 °C, and subsequent treatment with methylmagnesium bromide afforded the crude 1-phenoxycarbonyl-1,2-dihydropyridine.[11] The latter was converted to the *N*-Boc derivative **5** using *t*-BuOK at −60 °C in 91% overall yield for the two steps. Due to its low stability **5** was engaged without purification in a α-lithiation–iodation sequence[12] using *n*-BuLi and iodine to obtain, after an acidic workup, 6-iodo-2,3-dihydropyridin-4-one **4** in 76% yield.

Intermediate **4** was then involved in a Suzuki-type cross-coupling reaction[13] with various commercial boronic acids (Scheme 4). The use of aqueous condition[14] to improve the reactivity of the partners afforded derivatives **6** in good yields after standard flash chromatography performed on silica gel (Table 1).

The 6-chloro-3-pyridinyl moiety confers high potency to several types of compounds, like epibatidine[15] and synthetic analogues,[2] acting at the nAChRs. In order to incorporate this moiety on our dihydropyridinone structure, we have turned our attention to synthesise the requisite boronic acid.

Intermediate 5-bromo-2-chloropyridine **7**, easily obtained by a current Sandmeyer[16] procedure from 2-amino-5-bromopyridine, was engaged in a lithium–halogen exchange reaction, carried out in Et_2O at −78 °C using *n*-BuLi, followed by the reaction with $B(OiPr)_3$.[13] The desired boronic acid **8** is thus obtained with 78% yield after an appropriate mild acido-basic work up and an easy purification by recrystallisation (Scheme 5).[17]

Finally, protecting groups *t*-butoxycarbonyl were cleaved in acid conditions using trifluoroacetic acid to give the title 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones **2a–d** in high yields (Table 1).

In conclusion, we have developed an efficient new method for the synthesis of various substituted 6-(het)aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones, based on a fast and clean Suzuki cross-coupling reaction. The biological evaluation of these new compounds is now under investigation.

3. Experimental

3.1. General procedures

Commercial reagents were used as received without additional purification. Melting points were determined on a Köfler melting point apparatus and are uncorrected. IR spectra were taken with a Perkin–Elmer Spectrum BX FT-IR System spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in ppm downfield from the residual deuterated solvent or the internal standard tetramethylsilane. Thin layer chromatographies (TLC) were performed on 0.2 mm precoated plates of silica gel 60F-254 (Merck). Visualization was made with ultraviolet light (254 nm). Column chromatographies were carried out using silica gel 60 (0.063–0.2 mm) (Merck). Elemental analyses for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

3.1.1. *tert*-Butyl 6-iodo-2-methyl-1,2,3,4-tetrahydropyridine-1-carboxylate (4).[12a] To a stirred solution of 4-methoxypyridine (2.03 mL, 20.0 mmol) in dried THF, cooled to −25 °C, was added phenyl chloroformate (2.53 mL, 20.2 mmol, 1.01 equiv.). The resulting reaction mixture containing a white precipitate of pyridinium salts was allowed to react at this temperature over 1 h, at which point a solution of 3 M methylmagnesium bromide (7.0 mL, 21.0 mmol, 1.05 equiv.) was added dropwise. The reaction mixture was abandoned at −25 °C for 1 h, and then allowed to warm to room temperature under stirring for an additional hour. The mixture was quenched with water (50 mL) and extracted with diethyl ether (2×75 mL). The combined organic layers were then dried ($MgSO_4$) and the solvents removed in vacuo. The oily residue was dissolved in dry THF, cooled to −40 °C, and *t*-BuOK (8.98 g, 80.0 mmol, 4 equiv.) was added. The mixture was then abandoned at −40 °C for 2 h, and then allowed to warm to room temperature under stirring for an additional hour. Diethyl ether and water were then added to the mixture. The organic layer was separated, dried over $MgSO_4$ and concentrated to dryness to yield **5** (4.10 g, 91%) as a yellow oil. The residue was used without further purification in the next step. To a solution of **5** (4.06 g, 18.0 mmol) in freshly distilled THF, cooled to −60 °C, was added dropwise a solution of 2.5 M *n*-BuLi (8.64 mL, 21.6 mmol, 1.2 equiv.). The resulting mixture was allowed to react at this temperature over 30 min. A solution of iodine (5.03 g, 19.8 mmol, 1.1 equiv.) in THF was then added. The reaction mixture was abandoned at −60 °C for 2 h, and then allowed to warm to room temperature under stirring for an additional hour. The mixture was quenched by addition of 1 N HCl, extracted with diethyl ether, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel using diethyl ether/petroleum ether (4/6) as eluent to give **4** (4.61 g, 76%) as a yellow oil. IR (KBr): 2978, 2932, 1722, 1668, 1549, 1369, 1324, 1158, 1121 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.36 (s, 1H), 4.94 (m, 1H), 2.83 (dd, J=17.5, 5.9 Hz, 1H), 2.34 (d, J=17.5 Hz, 1H), 1.59 (s, 9H), 1.36 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 191.0, 151.4, 128.2, 109.8, 84.5, 53.2, 43.4, 28.1, 16.2. MS (EI) *m/z* (relative intensity) 337 ([$M^{+\cdot}$], 25), 280 (20), 263

(25), 237 (33), 236 (100), 221 (69), 193 (17), 165 (12), 110 (48), 84 (10).

3.1.2. 6-Chloropyridin-3-ylboronic acid (8). White solid (78%). Spectroscopic data corresponds to that reported in the literature.[17]

3.2. General procedure for the synthesis of *tert*-butyl 6-aryl-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-1-carboxylates (6a–d)

To a solution of **4** (500 mg, 1.48 mmol) in DME (10 mL) was added successively arylboronic acid (1.78 mmol, 1.2 equiv.), $Pd(PPh_3)_4$ (86 mg, 5 mol%) and a solution of $NaHCO_3$ (312 mg, 3.71 mmol, 2.5 equiv.) in water (5 mL). The reaction mixture was heated at reflux, TLC indicated complete conversion of the substrate (6 h). After cooling to room temperature, the mixture was extracted with $CHCl_3$ (2×15 mL), then the combined organic layers were dried over $CaCl_2$ and the solvents were removed in vacuo to leave the crude product which was purified by column chromatography on silica gel. Elution with diethyl ether–petroleum ether furnished **6a–d**.

3.2.1. *tert*-Butyl 2-methyl-4-oxo-6-(thien-2-yl)-1,2,3,4-tetrahydropyridine-1-carboxylate (6a). Yellow solid (87%), mp 90–91 °C. IR (KBr): 3087, 2973, 2933, 1718, 1659, 1584, 1424, 1389, 1308, 1227, 1160, 703 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.43 (d, J=4.9 Hz, 1H), 7.21 (d, J=3.3 Hz, 1H), 7.07 (dd, J=4.9, 3.3 Hz, 1H), 5.79 (s, 1H), 5.02 (m, 1H), 2.92 (dd, J=17.4, 5.8 Hz, 1H), 2.35 (d, J=17.4 Hz, 1H), 1.41 (d, J=7.0 Hz, 3H), 1.22 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 194.0, 152.9, 148.3, 141.5, 127.7, 127.5, 126.7, 112.5, 82.6, 51.3, 43.7, 27.5, 16.8. Anal. calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.34; H, 6.71; N, 4.86.

3.2.2. *tert*-Butyl 2-methyl-4-oxo-6-phenyl-1,2,3,4-tetrahydropyridine-1-carboxylate (6b). Beige solid (78%), mp 99 °C. IR (KBr): 3057, 3033, 2981, 2967, 2929, 1709, 1655, 1569, 1326, 1231, 1161, 768 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41–7.33 (m, 5H), 5.63 (s, 1H), 5.04 (m, 1H), 2.98 (dd, J=17.3, 5.9 Hz, 1H), 2.40 (d, J=17.3 Hz, 1H), 1.44 (d, J=7.0 Hz, 3H, CH_3), 1.08 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 194.1, 155.0, 152.6, 138.9, 129.7, 128.4, 126.1, 112.8, 82.5, 51.3, 43.6, 27.4, 16.7. Anal. calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.92; H, 7.51; N, 4.71.

3.2.3. *tert*-Butyl 6-(3-chlorophenyl)-2-methyl-4-oxo-1,2,3,4-tetra-hydropyridine-1-carboxylate (6c). Beige solid (78%), mp 101 °C. IR (KBr): 3022, 2968, 2931, 2876, 1714, 1674, 1582, 1562, 1478, 1396, 1368, 1311, 1153, 799 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.41–7.23 (m, 4H), 5.61 (s, 1H), 5.05 (m, 1H), 2.96 (dd, J=17.3, 5.8 Hz, 1H), 2.37 (d, J=17.3 Hz, 1H), 1.44 (d, J=6.8 Hz, 3H, CH_3), 1.12 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 193.9, 153.3, 152.2, 140.6, 134.4, 129.8, 129.5, 126.2, 124.3, 113.1, 82.8, 51.3, 43.5, 27.5, 16.7. Anal. calcd for $C_{17}H_{20}NO_3Cl$: C, 63.45; H, 6.26; N, 4.35. Found: C, 63.39; H, 6.36; N, 4.21.

3.2.4. *tert*-Butyl 6-(6-chloropyridin-3-yl)-2-methyl-4-oxo-1,2,3,4-tetra-hydropyridine-1-carboxylate (6d). Beige solid (80%), mp 115 °C. IR (KBr): 3038, 3003, 2969, 2932, 1711, 1660, 1592, 1455, 1406, 1369, 1317, 1235, 1154, 1087, 816 cm^{-1}. ^1H NMR ($CDCl_3$) δ 8.32 (d, J=2.4 Hz, 1H), 7.55 (dd, J=8.0, 2.4 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 5.57 (s, 1H), 5.03 (m, 1H), 2.93 (dd, J=17.2, 5.8 Hz, 1H), 2.36 (d, J=17.2 Hz, 1H), 1.49 (d, J=6.7 Hz, 3H, CH_3), 1.43 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 193.3, 152.1, 151.7, 150.4, 146.9, 136.0, 133.6, 123.9, 113.8, 83.4, 51.3, 43.3, 27.6, 16.7. Anal. calcd for $C_{16}H_{19}N_2O_3Cl$: C, 59.54; H, 5.93; N, 8.68. Found: C, 59.75; H, 5.88; N, 8.42.

3.3. General procedure for the synthesis of 6-aryl-2-methyl-2,3-dihydro-1*H*-pyridin-4-ones (2a–d)

To a solution of *tert*-butyl 6-aryl-2-methyl-4-oxo-1,2,3,4-tetrahydropyridine-1-carboxylate (0.85 mmol) in CH_2Cl_2 (5 mL), cooled to 0 °C, was added dropwise TFA (830 μL, 8.52 mmol, 10 equiv.). This mixture was stirred at room temperature until complete by TLC analysis (Et_2O/petroleum ether). Once complete (4 h) the reaction mixture was quenched with aqueous saturated K_2CO_3 solution, extracted with CH_2Cl_2, dried over $CaCl_2$, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using EtOAc as eluent to give **2a–d.**

3.3.1. 2-Methyl-6-(thien-2-yl)-2,3-dihydro-1*H*-pyridin-4-one (2a). Yellow solid (91%), mp 155–156 °C. IR (KBr): 3288, 3071, 2963, 2926, 1605, 1572, 1505, 1449, 1339, 1275, 1248, 1166, 769, 708 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45 (dd, J=5.1, 0.8 Hz, 1H), 7.43 (dd, J=3.7, 0.8 Hz, 1H), 7.11 (dd, J=5.1, 3.7 Hz, 1H), 5.50 (s, 1H), 5.24 (s, 1H), 3.94 (m, 1H), 2.46 (dd, J=16.1, 5.1 Hz, 1H), 2.37 (dd, J=17.4, 13.0 Hz, 1H), 1.41 (d, J=6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 193.0, 154.3, 137.9, 128.5, 128.1, 126.6, 97.8, 49.1, 43.5, 20.3. Anal. calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.24. Found: C, 62.34; H, 5.62; N, 7.02.

3.3.2. 2-Methyl-6-(phenyl)-2,3-dihydro-1*H*-pyridin-4-one (2b). Beige solid (92%), mp 161 °C. IR (KBr): 3268, 2971, 2934, 1605, 1580, 1511, 1449, 1387, 1348, 1271, 1167, 769, 694 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.54–7.52 (m, 5H), 5.39 (s, 1H), 5.04 (s, 1H), 3.94 (m, 1H), 2.46 (dd, J=16.2, 5.3 Hz, 1H), 2.38 (dd, J=16.2, 13.1 Hz, 1H), 1.41 (d, J=6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 193.2, 161.5, 135.7, 130.8, 128.9, 126.1, 98.5, 49.2, 43.3, 20.4. Anal. calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.21; H, 7.06; N, 7.22.

3.3.3. 6-(3-Chlorophenyl)-2-methyl-2,3-dihydro-1*H*-pyridin-4-one (2c). Beige solid (91%), mp 133 °C. IR (KBr): 3255, 3080, 2973, 2932, 2887, 1605, 1574, 1514, 1447, 1339, 1275, 1165, 782, 492 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.51–7.37 (m, 4H), 5.33 (s, 1H), 5.10 (s, 1H), 3.93 (m, 1H), 2.45 (dd, J=16.1, 4.8 Hz, 1H), 2.37 (dd, J=16.1, 13.1 Hz, 1H), 1.41 (d, J=6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 193.3, 160.0, 137.5, 134.9, 130.7, 130.3, 126.3, 124.2, 98.9, 49.3, 43.2, 20.3. Anal. calcd for $C_{12}H_{12}NOCl$: C, 65.02; H, 5.46; N, 6.32. Found: C, 65.15; H, 5.79; N, 6.13.

3.3.4. 6-(6-Chloropyridin-3-yl)-2-methyl-2,3-dihydro-1*H*-pyridin-4-one (2d). Beige solid (76%), mp 216 °C. IR (KBr): 3256, 3104, 2968, 2927, 2891, 1613, 1591, 1567, 1513, 1459, 1332, 1275, 1109, 796, 486 cm^{-1}. ^1H NMR (d6-DMSO) δ 8.65 (d, J=2.0 Hz, 1H), 8.07 (dd, J=8.3,

2.0 Hz, 1H), 7.69 (s, 1H), 7.61 (d, J=8.3 Hz, 1H), 5.15 (s, 1H), 3.78 (s, 1H), 2.28 (dd, J=15.9, 4.3 Hz, 1H), 2.16 (dd, J=15.9, 13.0 Hz, 1H), 1.29 (d, J=6.0 Hz, 3H). ^{13}C NMR (d_6-DMSO) δ 191.2, 157.0, 151.8, 147.9, 137.9, 130.3, 124.2, 97.0, 48.5, 42.9, 19.4. Anal. calcd for $C_{11}H_{11}N_2OCl$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.19; H, 5.08; N, 12.39.

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Samarium reagent-promoted formation of benzoins from diarylmethanones and DMF via a carbene rearrangement reaction

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Abstract—Prompted by samarium metal in DMF with TMSCl or iodine as an activator, or by SmI_2/THF system, diarylmethanones react readily with DMF to afford benzoins in moderate to good yields via rearrangement of aryl groups. As for asymmetric diarylmethanones, products resulting from the migration of either aryl group were obtained, where the migration of aryl groups shows certain priority.

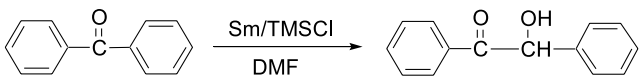
1. Introduction

Since the pioneering studies of Kagan and his co-workers demonstrated the particular effectiveness of samarium diiodide (SmI_2) as a powerful one-electron transfer reductant, the utilization of SmI_2 in synthetic organic synthesis has been widely documented.[1] Although samarium diiodide is a very useful reducing reagent, its application in organic synthesis is, to some extent, limited. Its storage is difficult due to its sensitivity to air oxidation. Besides, Sm^{2+} can only donate one electron in the reaction and the lack of atom economy seriously restricts its large scale application. Therefore, the direct use of metallic samarium as a reducing agent in organic transformations has attracted the attention of many organic chemists.[2] Usually, reactions promoted directly by samarium metal are carried out in THF,[3] and metallic samarium has to be activated by other reagents such as iodine, hydrochloric acid, alkyl halides, TMSCl, etc.[1,3,4] so as to ensure that the reactions proceed smoothly. We recently found that metallic samarium exhibits some interesting properties in organic synthesis when *N*,*N*-dimethylformamide (DMF) is used as a solvent instead of THF.[5]

The diarylmethanone dianion is a known species[6] whose reactions with carbonyl compounds or benzonitrile have long been observed.[7] Reduced by SmI_2, diarylmethanone readily forms ketyl, which has considerable stability and constitutes the important intermediate in cross-coupling reactions with ketones, aldehydes, imines, aroyl chlorides, conjugated carbon–carbon double bonds, and so on.[1]

2. Results and discussion

However, when diphenylmethanone was treated with samarium metal activated by TMSCl in DMF, surprisingly, benzoin was obtained in excellent yield (Scheme 1).



Scheme 1.

The unexpected formation of benzoin indicates that the additional carbonyl group comes from dimethylformamide, and the dimethylamino group acts as a leaving group in this reaction. Despite the fact that the carbonyl groups of amides are unreactive towards many carbon nucleophiles and are consequently employed as solvents in carbon–carbon bond-formation reactions,[8] DMF is well known for being a good formylation reagent (Vilsmeier–Haack reaction).[9] Besides, such necleophiles as Grignard reagents,[10a] organolithium[10a,b] and the radical anions[10c] resulting from the reduction by sodium in THF can attack the carbonyl group in DMF to afford the corresponding aldehydes. In the reactions mentioned above, the formoyl group in DMF was

Keywords: Samarium; DMF; Diarylmethanone; Rearrangement reaction; Benzoin; Benzil.
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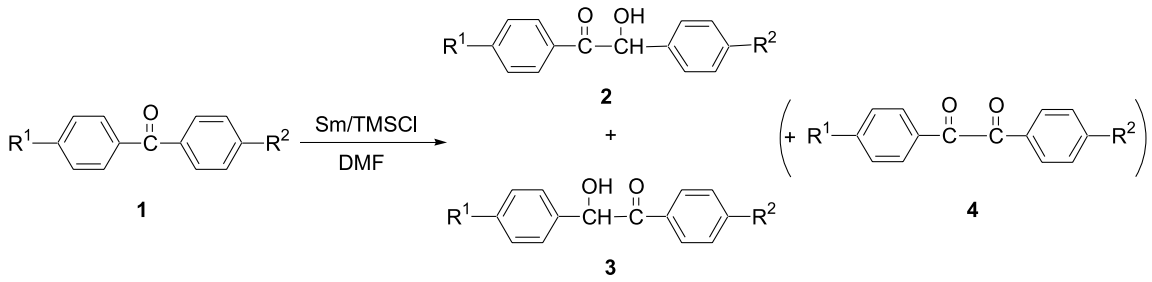


Scheme 2.

introduced into the products, with dimethylamino anion acting as a leaving group.

To have some idea about the mechanism of such a reaction, we carried out an extensive literature survey and were fortunate to find some clues to this reaction in the electron spin resonance study of the radicals obtained from acetophenone and benzaldehyde.[11] At high reduction potentials and by an irreversible electrode process, the conversion of acetophenone to 1-phenyl-propane-1,2-semidione in DMF was proposed to undergo a carbene rearrangement.[11b]

2.1. Sm/TMSCl-promoted formation of benzoin from diarylmethanone in DMF

To have an in-depth understanding of the reaction, a series of diarylketones were subjected to the same conditions and the desired benzoins were formed smoothly. In some cases, benzils were also obtained as unexpected byproducts (Scheme 2).

The results of the reactions are shown in Table 1.

The reaction of diarylketones with electron-donating group attached to the aromatic rings proceeded efficiently. In contrast, diarylketones with electron-withdrawing group require a relatively harsh reaction conditions and gave lower total yields. As can be seen, bis(*p*-methylphenyl)-methanone (**1b**) and bis(*p*-methoxyphenyl)-methanone (**1c**) produced 4,4′-dimethylbenzoin and anisoin, respectively (entries 2 and 3) in good yields, while bis(*p*-chlorophenyl)-methanone (**1e**) failed to afford the corresponding types of products **2** and **3**. It was surprising to find that bis(*p*-dimethylaminophenyl)-methanone (**1d**) did not undergo the reaction under the same conditions. The amino group might have some effects on TMSCl and thus bear an electron-withdrawing character, which made it difficult for the reaction to occur, as in the case of bis(*p*-chlorophenyl)-methanone (**1e**). As for asymmetric diarylmethanones, two kinds of benzoins could be obtained, with the carbonyl groups adjacent to the electron-richer aryl groups being predominant. This may indicate that the reaction followed a certain rule in the rearrangement.

It is worth noting that besides the 4′-chlorobenzoin (**3h**), benzoin (**2a**) was also obtained (entry 8). The formation of **2a** obviously resulted from a dechlorination process under the reaction conditions accompanying the rearrangement. As for phenyl *p*-bromophenyl methanone, the debromination reaction proceeded to such an extent that benzoin (**2a**) was isolated as the only product. Attempt was also made to investigate whether acetophenone and benzaldehyde could undergo such a reaction, but the result was negative.

2.2. Sm/I_2-promoted formation of benzoin from diarylmethanone in DMF

Considering that TMSCl is an acidic activator, we explored neutral activator iodine in our further investigations. To our delight, better results were obtained in the presence of I_2, as shown in Table 2.

With iodine as an activator, the reaction proceeded more easily in milder reaction conditions and produced higher total yields than that activated by TMSCl, except that substrate bis-(*p*-chlorophenyl)-methanone (**1e**) still failed to

Table 1. Reactions of diarylmethanones with DMF promoted by Sm/TMSCl in DMF

Entry	R^1, R^2 in substrate **1**	Temperature (°C)	Time (h)	Total yield of **2**, **3** (%)[a]	Ratio[b] of **2**/**3**	Yield of **4** (%)
1	H, H (**1a**)	90	10	91 (**2a**)		0 (**4a**)
2	4-CH_3, 4-CH_3 (**1b**)	80	6	74 (**2b**)		18 (**4b**)
3	4-CH_3O, 4-CH_3O (**1c**)	80	4	53 (**2c**)		35 (**4c**)
4	4-$(CH_3)_2N$, 4-$(CH_3)_2N$ (**1d**)	120	36	—		—
5	4-Cl, 4-Cl (**1e**)	120	12	—		—
6	4-CH_3, H (**1f**)	90	8	77 (**2f**, **3f**)	68/32	14 (**4f**)
7	4-Ph, H (**1g**)	80	5	47[c] (**2g**, **3g**)	19/81	16 (**4g**)
8	4-Cl, H (**1h**)	120	24	52[d] (**2a**, **3h**)	0/100	0
9	4-Br, H (**1i**)	120	24	53[e] (**2a**)		0

[a] Products **2** and **3** were inseparable and the overall yields were given.
[b] The ratio was determined by HPLC and ^{1}H NMR.
[c] A considerable amount of reductive product biphenyl-4-yl-phenyl-methanol was detected.
[d] Dechlorination reaction affording 26% of **2a** occurred simultaneously in the formation of the corresponding benzoin.
[e] Exclusive debromination product **2a** was formed.

Table 2. Reaction of diarylmethanones with DMF promoted by Sm/I_2 in DMF

Entry	R^1, R^2 in substrate **1**	Temperature (°C)	Time (h)	Total yield of **2**, **3** (%)	Ratio of **2/3**	Yield of **4** (%)
1	H, H (**1a**)	80	2	90 (**2a**)[12b]		0
2	4-CH_3, 4-CH_3 (**1b**)	70	1	79 (**2b**)[12b]		15 (**4b**)[12f]
3	4-CH_3O, 4-CH_3O (**1c**)	50	1	78 (**2c**)[12b]		16 (**4c**)[12f]
4	4-$(CH_3)_2N$, 4-$(CH_3)_2N$ (**1d**)	80	1	63 (**2d**)[12d]		21 (**4d**)[12f]
5	4-Cl, 4-Cl (**1e**)	120	5	—		—
6	4-CH_3, H (**1f**)	70	1	82 (**2f**, **3f**)[12c]	68/32	11 (**4f**)[12g]
7	4-Ph, H (**1g**)	50	1	87 (**2g**, **3g**)[12e]	81/19	9 (**4g**)[12h]
8	4-Cl, H (**1h**)	100	5	41 (**2h**, **3h**)[12c]	0/100	13 (**4h**)[12f]
9	4-Br, H (**1i**)	100	5	58 (**2a**)		0

give encouraging results (entry 5). Bis-(*p*-dimethylaminophenyl)-methanone, to our expectations, underwent the same kind of reactions under similar conditions and afforded the corresponding benzoin and benzil in high total yield (entry 4). The benzoins with the carbonyl groups adjacent to the electron-richer aryl groups still predominated in the products when asymmetric diarylmethanones were used as substrates under the $Sm/DMF/I_2$ conditions. An exception was that biphenyl-4-yl-phenyl-methanone (**1g**) produced the benzoin with the carbonyl group adjacent to the biphenyl group as the major product (entry 7). However, the relationship between the reaction chemoselectivity and activator remains unclear.

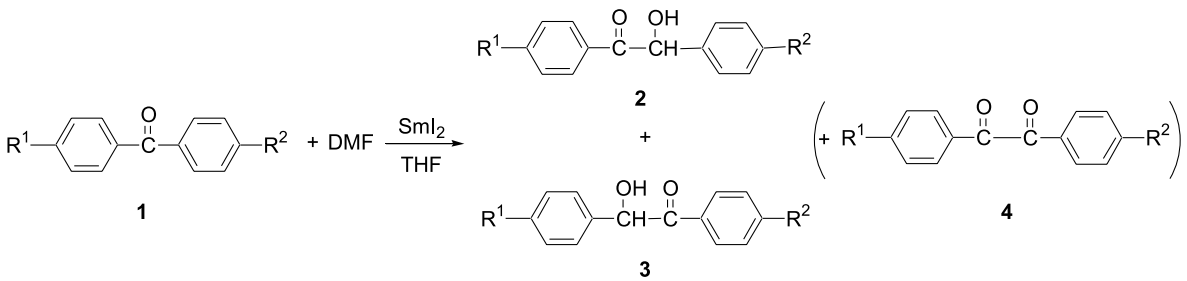
2.3. SmI_2-promoted formation of benzoin from diarylmethanone and DMF in THF

We made the attempt and found that without activator (TMSCl or I_2) the reaction could not occur at all, and further attempts to expand the reaction to other metal such as zinc failed. We also tried other solvents instead of DMF, such as THF, DMSO and toluene, but did not detect any formation of benzoin. This result may indicate that the additional carbonyl group came from DMF.

Therefore, we made further investigations to find out whether or not SmI_2 can promote the coupling rearrangement reaction of diarylmethanone and DMF in THF. To our expectations, the reaction occurred smoothly and completed in a very short time, despite a relatively low total yield and more byproduct benzil (Scheme 3, Table 3). The chemoselectivity of rearrangement reaction is generally similar to that in the $Sm/DMF/I_2$ system.

2.4. Possible mechanism

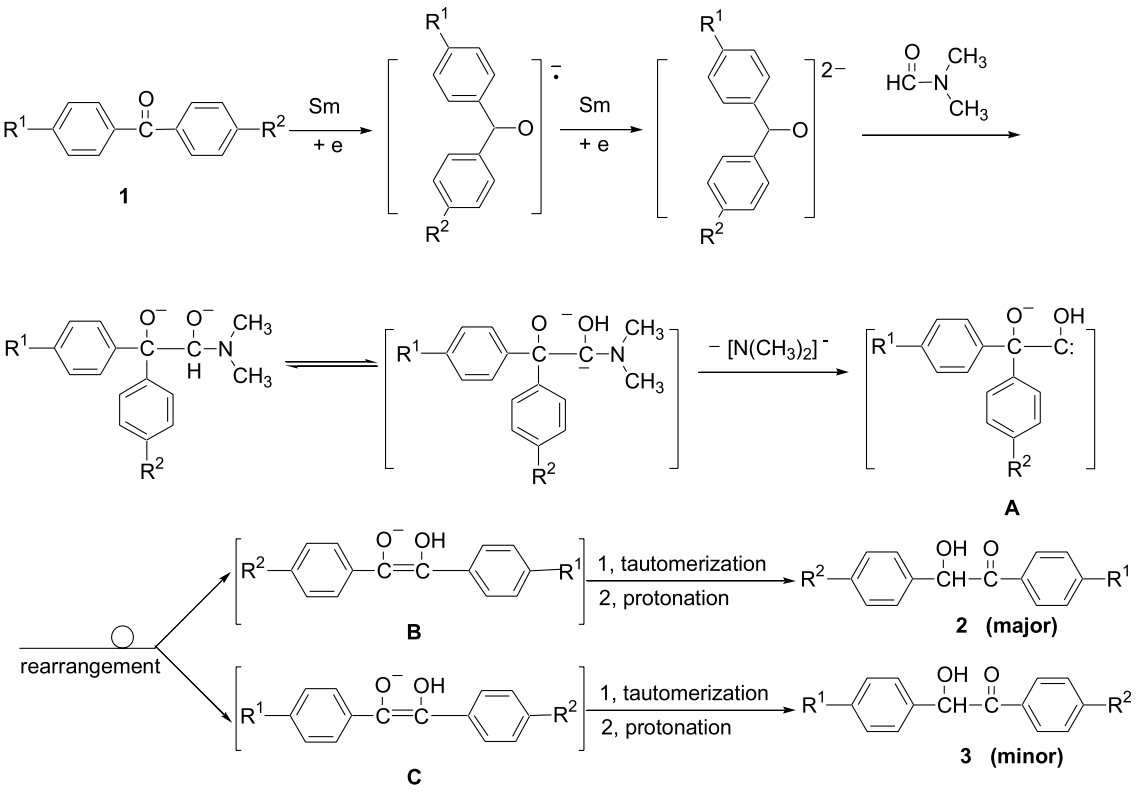
The formation of benzils could be explained as a result of the auto-oxidation of benzoins. The presence of reports claiming that some metal salts such as copper (I)[13a] and Ce (IV)[13b] could easily catalyze the autoxidation of benzoins into the corresponding benzils made us deduce that the presence of samarium salts might have accelerated the formation of benzils from benzoins during the treatment process. Further investigations showed that the benzil



Scheme 3.

Table 3. Reaction of diaryl-methanones with DMF promoted by SmI_2 in THF

Entry	R^1, R^2 in substrate **1**	Total yield of **2**, **3** (%)	Ratio of **2/3**	Yield of **4** (%)
1	H, H (**1a**)	42 (**2a**)		39 (**4a**)[12f]
2	4-CH_3, 4-CH_3 (**1b**)	29 (**2b**)		51 (**4b**)
3	4-CH_3O, 4-CH_3O (**1c**)	48 (**2c**)		36 (**4c**)
4	4-$(CH_3)_2N$, 4-$(CH_3)_2N$ (**1d**)	33 (**2d**)		31 (**4d**)
5	4-Cl, 4-Cl (**1e**)	0		0
6	4-CH_3, H (**1f**)	42 (**2f**, **3f**)	71/29	31 (**4f**)
7	4-Ph, H (**1g**)	27 (**2g**, **3g**)	78/22	39 (**4g**)
8	4-Cl, H (**1h**)	0		0
9	4-Br, H (**1i**)	0		0



Scheme 4.

could also have been obtained when benzoin was treated under the same reaction conditions. This validates our suggestion.

We made the attempt and found that without activator (TMSCl or I_2) the reaction could not occur at all, and further attempts to expand the reaction to other metal such as zinc failed. On the other hand, the fact that without diarylmethanone in the reaction system, no obvious reaction between Sm/activator and DMF was observed shows the reaction must be initiated by ketyl resulting from diarylmethanone. Based on our experimental results and the ESR studies on the relevant radicals,[11b] a possible mechanism is suggested (Scheme 4).

Due to the strongly electrophilic character of carbene,[14] **A** undergoes a rearrangement (intramolecular insertion reaction) in which the electron-richer aryl group of the two preferably migrates to form enol intermediates (**B**>**C**), which in turn tautomerize immediately, and are followed by protonation to give the corresponding benzoins, respectively.

In conclusion, with TMSCl or iodine as the activator in DMF or performed in SmI_2/THF system, the reaction between diarylketones and DMF via a rearrangement process promoted by samarium metal can afford benzoins and benzils in good overall yields. The complexing of DMF with samarium ion[15] may have played an important role in enabling the reaction to occur, and studies on the exact mechanism are currently in progress.

3. Experimental

3.1. General

All ^{1}H NMR spectra were measured in $CDCl_3$ and recorded on Brucker Avance-400 (400 MHz) spectrometer with TMS as the internal standard. Chemical shifts are expressed in ppm and *J* values are given in Hz. IR spectra were run on a Bruck vector 22 spectrometer. EI-MS were determined with a HP5989B mass spectrometer. Melting points are uncorrected. All the reactions in this paper were performed under nitrogen atmosphere. DMF was redistilled and dried over molecular sieve before use.

3.2. Sm/DMF/TMSCl system promoted rearrangement reaction of diarylketones with DMF

General procedure. To a mixture of Sm powder (2 mmol) and diarylketone (2 mmol) in freshly distilled *N*,*N*-dimethylformamide (DMF, 10 mL) TMSCl (0.2 mL, freshly distilled) was added at room temperature, with magnetic stirring under a nitrogen atmosphere. The reaction mixture was then heated to a certain temperature so as to ensure that the reaction occurred (as indicated in Table 1). After the completion of the reaction (monitored by TLC), dilute hydrochloric acid (2 M, 5 mL) was added and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude products were purified with flash chromatography (silica/hexanes–ethyl

acetate, 9:1 v/v) to afford the corresponding benzoins and/or benzils.

3.3. Sm/DMF/I_2 system promoted rearrangement reaction of diarylketones with DMF

General procedure. To a mixture of Sm powder (2 mmol) and diarylketone (2 mmol) in freshly distilled *N*,*N*-dimethylformamide (DMF, 10 mL) I_2 (0.13 g, 0.5 mmol) was added at room temperature, with magnetic stirring under a nitrogen atmosphere. The reaction mixture was then heated to a certain temperature so as to ensure that the reaction occurred (as indicated in Table 2). After the completion of the reaction (monitored by TLC), dilute hydrochloric acid (2 M, 5 mL) was added and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude products were purified with flash chromatography (silica/hexanes–ethyl acetate, 9:1 v/v) to afford the corresponding benzoins and/or benzils.

3.4. SmI_2/THF system promoted rearrangement reaction of diarylketones with DMF

General procedure. To a solution of SmI_2 (3 mmol) in THF (20 mL), diarylketone (1 mmol) was added at room temperature under a nitrogen atmosphere. The deep blue color of the solution turned red immediately, and DMF (0.5 mL) was added. The color of resultant solution vanished immediately, which indicated that the reaction had completed. After being stirred for 5–10 min, dilute hydrochloric acid (2 M, 5 mL) was added and the resulting mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The crude products were purified with flash chromatography (silica/hexanes–ethyl acetate, 9:1 v/v) to afford the corresponding benzoins and/or benzils.

3.4.1. 2-Hydroxy-1,2-diphenyl-ethanone (2a). White solid, mp 134–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.95 (m, 2H), 7.52–7.54 (m, 1H), 7.40–7.44 (m, 2H), 7.28–7.36 (m, 5H), 5.97 (d, 1H, J=6.0 Hz), 4.56 (d, 1H, J=6.0 Hz); IR (KBr) 3417, 3060, 2933, 1680, 1596, 1491, 1450 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 213 (1.16, M^++1), 212 (0.43, M^+), 195 (13.95, M^+−OH), 107 (61.01), 105 (100), 77 (89.62). Anal. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.48; H, 5.74.

3.4.2. 2-Hydroxy-1,2-di-*p*-tolyl-ethanone (2b). White solid, mp 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.85 (m, 2H), 7.19–7.24 (m, 4H), 7.13–7.15 (m, 2H), 5.91 (d, 1H, J=6.0 Hz), 4.55 (d, 2H, J=6.0 Hz), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR δ ($CDCl_3$): 198.6, 144.9, 138.3, 136.4, 131.0, 129.8, 129.4, 129.3, 127.7, 75.8, 21.7, 21.2; IR (KBr) 3473, 3038, 2921, 1676, 1607, 1513 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 241 (0.36, M^++1), 240 (1.20, M^+), 223 (1.79, M^+−OH), 121 (85.90), 119 (95.45, M^+), 91 (100). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.68; H, 6.73.

3.4.3. 2-Hydroxy-1,2-bis-(4-methoxyphenyl)-ethanone (2c). White solid; mp 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.94 (m, 2H), 7.25–7.28 (m, 2H), 6.85–6.90 (m, 4H), 5.87 (d, 1H, J=5.2 Hz), 4.60 (d, 1H, J=5.2 Hz), 3.84 (s, 3H), 3.78 (s, 3H); ^{13}C NMR δ ($CDCl_3$): 197.3, 164.0, 159.6, 132.4, 131.9, 131.6, 129.0, 114.5, 113.9, 75.3, 55.5, 55.2; IR (KBr) 3465, 3077, 2939, 1667, 1598, 1514, 1469 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 272 (0.61, M^+), 255 (0.88, M^+−OH), 137 (100), 135 (86.2), 107 (17.31), 77 (80.38). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.89; H, 5.88.

3.4.4. 1,2-Bis-(4-dimethylamino-phenyl)-2-hydroxy-ethanone (2d). White solid; mp 153–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.88 (m, 2H), 7.20–7.22 (m, 2H), 6.66–6.68 (m, 4H), 5.80 (d, 1H, J=6.0 Hz), 4.68 (d, 1H, J=6.0 Hz), 2.92 (s, 6H), 3.03 (s, 6H); ^{13}C NMR δ ($CDCl_3$): 196.6, 154.2, 153.6, 132.2, 131.5, 128.6, 110.8, 110.6, 74.9, 40.1, 39.9; IR (KBr) 3420, 2916, 1681, 1595, 1546, 1483 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 298 (0.24, M^+), 150 (2.16), 148 (100), 120 (5.51). Anal. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.54; H, 7.50; N, 9.45.

3.4.5. 2-Hydroxy-2-phenyl-1-*p*-tolyl-ethanone (2f). The title compound was obtained as a mixture with **3f**; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.85 (m, 2H), 7.14–7.35 (m, 7H), 5.94 (d, 1H, J=6.0 Hz), 4.61 (d, 1H, J=6.0 Hz), 2.38 (s, 3H); IR (KBr) 3441, 3059, 2945, 1675, 1607, 1510, 1491, 1452, 1390 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 227 (0.28, M^++1), 226 (0.72, M^+), 209 (2.59, M^+−OH), 119 (100), 107 (10.37), 91 (55.09), 77 (57.75). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.48; H, 6.28.

3.4.6. 2-Hydroxy-1-phenyl-2-*p*-tolyl-ethanone (3f). The title compound was obtained as a mixture with **2f**; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.95 (m, 2H), 7.15–7.37 (m, 7H), 5.94 (d, 1H, J=6.0 Hz), 4.52 (d, 1H, J=6.0 Hz), 2.31 (s, 3H); IR (KBr) 3441, 3059, 2945, 1675, 1607, 1510, 1491, 1452, 1390 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 227 (0.28, M^++1), 226 (0.72, M^+), 209 (2.59, M^+−OH), 121 (82.30), 105 (24.30), 91 (55.09), 77 (57.75). Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.48; H, 6.28.

3.4.7. 1-Biphenyl-4-yl-2-hydroxy-2-phenyl-ethanone (2g). The title compound was obtained as a mixture with **3g**; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–8.03 (m, 2H), 7.29–7.65 (m, 12H), 6.00 (d, 1H, J=6.0 Hz), 4.60 (d, 1H, J=6.0 Hz); IR (KBr) 3422, 3031, 1678, 1603, 1560, 1487, 1450, 1407 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 181 (38.10), 153 (19.85), 107 (6.91), 77 (100). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.10; H, 5.56.

3.4.8. 2-Biphenyl-4-yl-2-hydroxy-1-phenyl-ethanone (3g). The title compound was obtained as a mixture with **2g**; white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–8.00 (m, 2H), 7.29–7.65 (m, 12H), 6.02 (d, 1H, J=6.0 Hz), 4.59 (d, 1H, J=6.0 Hz); IR (KBr) 3422, 3031, 1678, 1603, 1560, 1487, 1450, 1407 cm^{-1}; mass spectrum, *m*/*z* (relative intensity, %) 183 (32.29), 153 (19.85), 105 (28.57), 77

(100). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.10; H, 5.56.

3.4.9. 2-(4-Chloro-phenyl)-2-hydroxy-1-phenyl-ethanone (3h). White solid; mp 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.92 (m, 2H), 7.54–7.57 (m, 1H), 7.28–7.46 (m, 6H), 5.96 (d, 2H, J=6.0 Hz), 4.56 (d, 1H, J=6.0 Hz); IR (KBr) 3417, 3027, 1679, 1618, 1596, 1450 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 248 (0.07, M^++2), 246 (0.20, M^+), 229 (0.55, M^+−OH), 141 (13.71), 105 (100), 77 (76.76). Anal. Calcd for $C_{14}H_{11}ClO_2$: C, 68.16; H, 4.50. Found: C, 68.28; H, 4.47.

3.4.10. 1,2-Di-phenyl-ethane-1,2-dione (4a). Yellow crystal (CCl_4); mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–7.99 (4H, m), 7.64–7.69 (2H, m), 7.50–7.53 (4H, m); IR (KBr): 3064, 1660, 1594, 1450, 1211, 719, 643 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 210 (1.77, M^+), 105 (100), 77 (45.51). Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.99; H, 4.79. Found: C, 80.10; H, 4.80.

3.4.11. 1,2-Di-*p*-tolyl-ethane-1,2-dione (4b). Yellow crystal (CCl_4); mp 101–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.89 (m, 4H), 7.31–7.33 (m, 4H), 2.45 (s, 6H); ^{13}C NMR δ ($CDCl_3$): 194.5, 146.1, 130.7, 130.0, 129.7, 21.9; IR (KBr) 3063, 2919, 1662, 1605, 1573, 1447, 1410 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 239 (0.37, M^++1), 238 (1.84, M^+), 119 (100), 91 (40.17). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.48; H, 5.90.

3.4.12. 1,2-Bis-(4-methoxyphenyl)-ethane-1,2-dione (4c). Yellow crystal (CCl_4); mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.98 (m, 4H), 6.98–7.00 (m, 4H), 3.91 (s, 6H); ^{13}C NMR δ ($CDCl_3$): 193.5, 164.9, 132.4, 126.3, 114.3, 55.6; IR (KBr) 3026, 2959, 1656, 1600, 1573, 1510, 1458 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 271 (0.16, M^++1), 270 (0.87, M^+), 135 (100), 107 (13.77). Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.48; H, 5.30.

3.4.13. 1,2-Bis-(4-dimethylamino-phenyl)-ethane-1,2-dione (4d). Yellow crystal (CCl_4); mp 201–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.89 (m, 4H), 6.57–6.59 (m, 4H), 3.09 (s, 12H); ^{13}C NMR δ ($CDCl_3$): 194.0, 169.1, 121.6, 121.1, 112.8, 40.5; IR (KBr) 2916, 1644, 1595, 1546, 1483 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 297 (1.41, M^++1), 296 (6.48, M^+), 148 (100), 120 (5.51). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.62; H, 6.77, 9.41.

3.4.14. 1-Phenyl-2-*p*-tolyl-ethane-1,2-dione (4f). Yellow crystal (CCl_4); mp 30–31 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97–8.00 (m, 2H), 7.87–7.90 (m, 2H), 7.64–7.67 (m, 1H), 7.50–7.54 (m, 2H), 7.30–7.34 (m, 2H), 2.45 (s, 3H); IR (KBr) 3062, 2924, 1672, 1605, 1581, 1450 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 225 (0.23, M^++1), 224 (0.95, M^+), 119 (100), 105 (38.86), 91 (45.30), 77 (31.63). Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.38; H, 5.38.

3.4.15. 1-Biphenyl-4-yl-2-phenyl-ethane-1,2-dione (4g). Yellow crystal (CCl_4); mp 103–105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02–8.09 (m, 4H), 7.75–7.77 (m, 2H), 7.65–7.70 (m, 3H), 7.49–7.57 (m, 5H); ^{13}C NMR δ ($CDCl_3$): 194.6, 194.2, 147.6, 139.5, 134.9, 133.0, 131.7, 130.5, 130.0, 129.1, 128.7, 127.7, 127.4, 127.3; IR (KBr) 3062, 1673, 1594, 1580, 1485, 1449 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 287 (0.16, M^++1), 286 (0.51, M^+), 181 (100), 153 (22.18), 105 (22.77), 77 (33.18). Anal. Calcd for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.75; H, 4.97.

3.4.16. 1-(4-Chloro-phenyl)-2-phenyl-ethane-1,2-dione (4h). Yellow crystal (CCl_4); mp 73–74 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–8.16 (m, 4H), 7.52–7.60 (m, 5H); IR (KBr) 3023, 1679, 1139, 1609, 1596, 1450 cm^{-1}; mass spectrum, *m/z* (relative intensity, %) 246 (0.18, M^++2), 244 (0.55, M^+), 139 (13.65), 105 (100), 77 (66.67). Anal. Calcd for $C_{14}H_9ClO_2$: C, 68.72; H, 3.71. Found: C, 68.58; H, 3.77.

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A convenient synthesis of 1′-*H*-spiro-(indoline-3,4′-piperidine) and its derivatives

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Abstract—A simple synthetic route has been developed to prepare 1′-*H*-spiro(indoline-3,4′-piperidine) (**1d**). Dialkylation of 2-fluorophenylacetonitrile with *N*-(*tert*-butyloxycarbonyl)-bis(2-chloroethyl)amine (**5**) gave **6**. Deprotection of Boc followed by cyclization resulted **1d** in 67% overall yield. Selective Boc or Cbz protection of 1′-*N* gave **1a** or **1b** with 90 and 85% yield, respectively. Thus, in a five-step procedure, **1a** and **1b** were synthesized from commercially available reagents in over 50% overall yield. All 3 compounds (**1a**, **1b** and **1d**) can be utilized as templates to synthesize compounds for GPCR targets.

1. Introduction

In the past few years, spiro-piperidines have received great attention because of their promising therapeutic application.[1–4] The spiro(indoline-3,4′-piperidine) scaffold is a key structural feature in **2** (MK-0677), a potent peptidomimetic growth hormone secretagogue (GHS);[5] **3**, a serine derived NK_1 antagonist;[6] and **4**, a potent and selective melanocortin subtype-4 (MC-4) receptor agonist.[7] It is also found in oxytocin, somatostatin, tachykinines, anaphylatoxin chemotactic receptor ligands, and is considered as a privileged structure for general G-protein coupled receptor (GPCR) ligands (Fig. 1).[8]

We were particularly interested in synthesizing multiple grams of 1′-*H*-spiro-(indoline-3,4′-piperidine) (**1d**), and its derivatives **1a** and **1b**, where the 1′-*N* is selectively protected by a Boc or Cbz group, respectively. These three compounds can all serve as convenient starting material for two-point diversity parallel synthesis. The only literature directly related to preparation of **1a** was reported by Chen et al.[9] involving a six-step synthesis which gave a low overall yield (<10%). Thus, this route was less attractive for large-scale synthesis.

Several methods have been published for the synthesis of other spiro(indoline-3,4′-piperidine) analogs. The Fischer indole type synthetic approach reported by Maligres et al. yielded **1b**, a 1′-Cbz-protected analog with an overall yield of 80% in five steps, but based on quantitative HPLC analysis only.[10] The two-step synthesis of 1′-methylated analog (**1c**) reported by Ong (Scheme 1) seemed to be straightforward;[11] however, in our hands, only a 20% overall yield was achieved. Subsequent 1′-*N*-demethylation with α-chloroethyl chloroformate (ACE-Cl)[12] also proved to be problematic, further limiting the use of this chemistry for our needs.[13] However, during the investigation of these routes, we identified an efficient method to generate **1d** using a modified approach for the synthesis of **1c**.

Our synthetic route is illustrated in Scheme 2. *N*-(*tert*-butyloxycarbonyl)-bis(2-chloroethyl)amine (**5**) was prepared from commercially available bis-(2-chloroethyl)-amine hydrochloride.[4] Dialkylation of 2-fluorophenyl-acetonitrile with **5** followed by deprotection of the Boc group afforded **7** in 70% yield.[2] Our initial attempt to prepare **7** directly from bis-(2-chloroethyl)amine hydrochloride without N-protection failed. Reduction of **7** with LAH and spontaneous cyclization gave **1d** in 95% yield. Finally, selective protection of **1d** at 1′-*N* with Boc_2O gave **1a** in 90% yield. Based on our experience, it was not successful to generate **1a** from **6** directly using LAH reduction because of concomitant reduction of the Boc group. In the meantime, **1b** was obtained by protection of **1d** with *N*-(benzyloxycarbonyloxy)succinimide (Z–OSu) in 85% yield.

In conclusion, we have developed a convenient synthesis of 1′-*H*-spiro-(indoline-3,4′-piperidine) (**1d**), which was obtained in 67% yield in four steps from commercially available reagents. Its versatile derivatives **1a** and **1b** were obtained in over 50% overall yield with an additional

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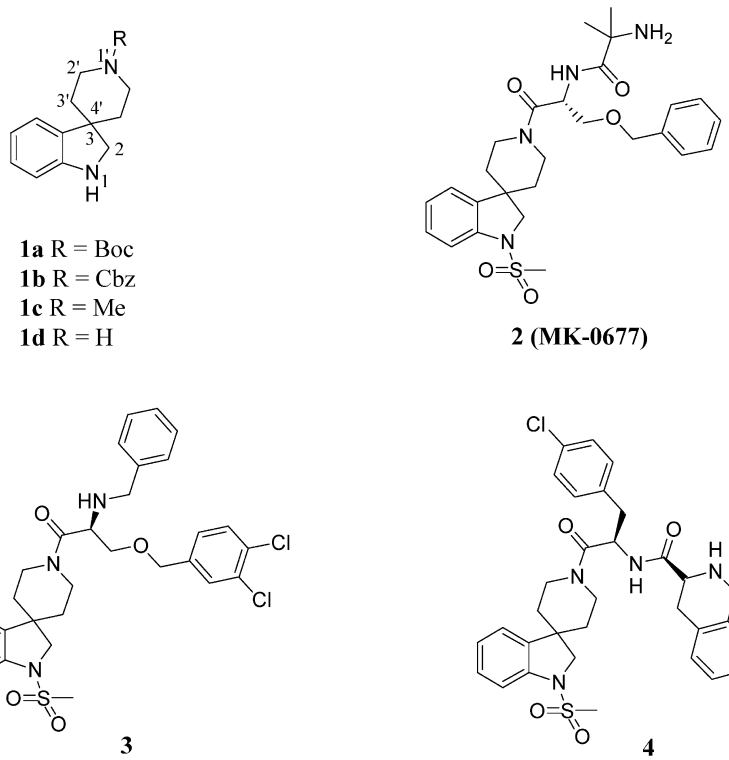
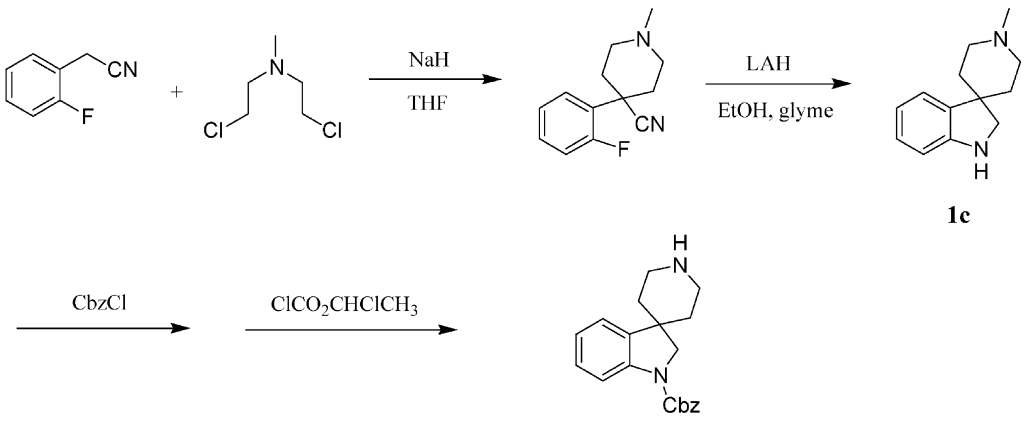


Figure 1.



Scheme 1.

selective protection step. All three compounds (**1a**, **1b** and **1d**) can be used in the parallel synthesis of compound libraries targeting GPCRs.[14]

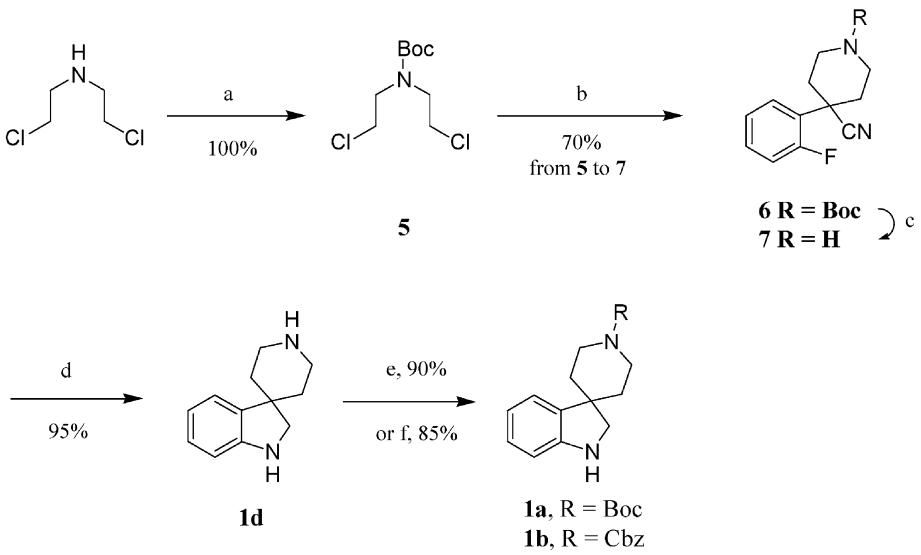
2. Experimental

2.1. General

^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Bruker AM 500 spectrometer in $CDCl_3$ solutions using TMS or $CDCl_3$ as the internal standard. CI mass spectra were performed with a PE API 2000 LC/MS/MS spectrometer. Elemental analyses were determined with a Perkin–Elmer 2400 series CHNS Analyzer. Melting points were observed with a Lab-Devices Mel-Temp II micro melting point apparatus (hot-plate type). EM Science silica gel 60 (230–400 mesh ASTM) was used for flash column chromatography. Anhydrous THF was distilled from sodium/benzophenone under nitrogen. All chemical reagents were purchased from Acros China.

2.2. Practical synthesis of 1′-*H*-spiro-[indoline-3,4′-piperidine] (1d) and its derivatives 1a and 1b

2.2.1. *N*-(*tert*-Butyloxycarbonyl)-bis(2-chloroethyl)-amine (5). The protection of bis-(2-chloroethyl)amine hydrochloride (42 g, 240 mmol) with di-*tert*-butyl dicarbonate (62 g, 280 mmol) was carried out based on the reference procedure.[4] The crude product was run through a pad of silica gel (petroleum ether/ethyl ether, 1:1) to yield **5** as a pale yellow oil (60 g, quantitative yield) (lit.[4] yield 88%). CI-MS *m/e* 242/244 (M+H).



Scheme 2. Reagents: (a) $(Boc)_2O/Et_3N$; (b) 2-fluorophenylacetonitrile/NaH/THF; (c) 8 M HCl/dioxane; (d) $LiAlH_4$/EtOH/glyme; (e) $Boc_2O/Et_3N/CH_2Cl_2$; (f) Z-OSu/THF.

2.2.2. 4-Cyano-4-(2-fluorophenyl)-1-*N*-(*tert*-butyloxycarbonyl)piperidine (6). To a solution of 2-fluorophenyl-acetonitrile (25 g, 180 mmol) in 300 mL anhydrous THF was added with vigorous stirring sodium hydride (60% in mineral oil) (47 g). The temperature of the reaction mixture was carefully kept below 5 °C. The ice water bath was removed after the addition, and the reaction mixture was allowed to warm to room temperature and stirred at the temperature for 30 min. The reaction mixture was then cooled to 0 °C and **5** (30 g, 120 mmol) was added. The reaction mixture was slowly warmed to reflux and then refluxed for 3 h. After refluxing, the reaction mixture was concentrated to remove the THF and to the recovered reaction mixture was added ice water slowly, followed by extraction with ether 3 times. The ether layers were combined and washed with water, dried with magnesium sulfate, filtered, and concentrated to yield the crude product as a yellow solid, which contained small amount of unreacted 2-fluorophenyl-acetonitrile. The yellow solid was recrystalized from ethyl acetate to give **6** as a white solid (48 g, 160 mmol). A small amount of analytical sample was prepared by purification of the above solid with a flash chromatography column and recrystalization: mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.47 (s, 9H), 2.08 (dd, 2H), 2.19 (d, J=12.3 Hz, 2H), 3.22 (m, 2H), 4.24 (m, 2H), 7.12 (dd, 1H), 7.18 (dd, 1H), 7.33–7.38 (m, 1H), 7.45 (dd, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.55, 33.98, 40.38, 41.01, 80.31, 117.2 (d, J=25 Hz), 120.4, 124.9, 126.5, 127.2, 130.5, 154.6, 160.9 (d, J=250 Hz); CI-MS *m/e* 305 (M+H). Anal. Calcd for $C_{17}H_{21}N_2O_2F$: C, 67.09; H, 6.95; N, 9.20. Found C, 67.09; H, 6.86; N, 9.23.

2.2.3. 4-Cyano-4-(2-fluorophenyl)piperidine (7). A mixture of **6** (48 g, 160 mmol) in dioxane-8 M HCl solution was refluxed for 30 min. The reaction mixture was concentrated to dryness and water (280 mL) was added. The mixture was washed with ether until no starting material could be detected by HPLC. The mixture was then adjusted to pH=9 and the aqueous layer was extracted by ether. The ether layers were combined, back washed with water, dried with magnesium sulfate, concentrated to dryness to give **7**, which was obtained as a white crystalline solid (17 g, 84 mmol, 70% from **5** to **7**): mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.08–2.14 (m, 2H), 2.22 (d, J=13.3 Hz, 2H), 3.14–3.20 (m, 4H), 7.12 (dd, 1H), 7.16 (dd, 1H), 7.31–7.36 (m, 1H), 7.45 (dd, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.03, 40.39, 43.72, 117.0 (d, J=25 Hz), 121.1, 124.8 (d, J=12.5 Hz), 127.1, 127.4, 130.1 (d, J=12.5 Hz), 160.9 (d, J=250 Hz); CI-MS *m/e* 205 (M+H). Anal. Calcd for $C_{12}H_{13}N_2F$: C, 70.57; H, 6.42; N, 13.72. Found C, 70.23; H, 6.32; N, 13.70.

2.2.4. 1′-*H*-Spiro-[indoline-3,4′-piperidine] (1d). To glyme (360 mL) was added LAH (15 g, 400 mmol). The reaction mixture was cooled to 0 °C and anhydrous ethanol (36 mL) was added slowly while keeping the reaction temperature around 0 °C. The ice bath was removed, and the mixture was slowly heated to reflux. To the above reaction mixture was added **7** (17 g, 84 mmol) in 200 mL glyme. The reaction mixture was refluxed for 72 h, cooled to 0 °C and water was slowly added with vigorous stirring. The precipitate was filtered, rinsed with dichloromethane a few times. The filtrates were combined, dried with anhydrous potassium carbonate, filtered, concentrated to dryness to give **1d** as a white crystalline solid (15 g, 80 mmol, 95%): mp 140–142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.71 (d, 2H), 2.19 (d, J=13.3 Hz, 2H), 1.79 (dd, 2H), 2.74 (dd, 2H), 3.05 (d, J=12.6 Hz, 2H), 3.47 (s, 2H), 6.63 (d, J=7.7 Hz, 1H), 6.74 (dd, 1H), 7.04 (dd, 1H), 7.08 (d, J=7.41 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.85, 43.69, 44.85, 56.65, 109.7, 118.8, 122.7, 127.8, 137.3, 150.6; CI-MS *m/e* 189 (M+H). Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found C, 76.65; H, 8.52; N, 14.49.

2.2.5. 1′-Boc-spiro-[indoline-3,4′-piperidine] (1a). To a solution of **1d** (18.8 g, 100 mmol) in triethylamine (10 g, 100 mmol) and dichloromethane (250 mL) was slowly added a solution of di-*tert*-butyl dicarbonate (22 g, 100 mmol) in dichloromethane (250 mL). The reaction mixture was stirred at room temperature for 2 h, washed with saturated sodium bicarbonate solution and brine. The organic layer was dried with sodium sulfate, filtered and

concentrated to yield a crude solid. The solid was triturated with 50% ethyl acetate–hexane to give **1a** as a white solid (26 g, 90 mmol, 90%): mp 173–174 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.49 (s, 9H), 1.71 (d, J=13.1 Hz, 2H), 1.81 (m, 2H), 2.92 (m, 2H), 3.48 (s, 2H), 4.06 (m, 2H), 6.65 (d, J=7.5 Hz, 1H), 6.75 (dd, 1H), 7.03–7.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 28.65, 35.71, 41.20, 44.60, 56.10. 79.69, 109.9, 118.9, 122.8, 128.1, 136.5, 150.7, 155.1; CI-MS *m/e* 289 (M+H). Anal. Calcd for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71. Found C, 70.49; H, 8.11; N, 9.55.

2.2.6. 1′-Cbz-spiro-[indoline-3,4′-piperidine] (1b). To a solution of **1d** (3.0 g, 16 mmol) in anhydrous THF (16 mL) was slowly added Z–OSu (4.0 g, 16 mmol). The reaction mixture was stirred at room temperature for 2 h, then concentrated to dryness. The crude product was partitioned between ethyl acetate and 1 N NaOH aqueous solution. The organic layer was then washed with saturated sodium bicarbonate solution and brine, dried with sodium sulfate, filtered and concentrated to yield a crude solid. The solid was triturated with MeOH to give **1b** as a white solid. (4.5 g, 14 mmol, 85%): mp 115–117 °C (lit.[10] mp 118–120 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.73–1.82 (m, 4H), 3.01 (m, 2H), 3.50 (s, 2H), 4.13 (m, 2H), 5.16 (s, 2H), 6.71 (d, J=7.8 Hz, 1H), 6.80 (dd, 1H), 7.32–7.38 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.56, 41.41, 44.51, 56.06, 67.24, 109.9, 118.9, 122.7, 128.0, 128.1, 128.6, 136.2, 137.0, 150.6, 155.5; CI-MS *m/e* 323.0 (M+H). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found C, 74.38; H, 7.07; N, 8.59.

Acknowledgements

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13. Based on the in-house experiment, the 1′-*N*-demethylation using α-chloroethyl chloroformate (ACE–Cl) gave a complex reaction mixture with the desired product in 50% conversion based on HP LC/MS. The impurities were not identified.
14. Based on the in-house experiment, the 1′-*N* of **1d** can selectively react with acid chloride, acid anhydride, chloroformate and sulfonyl chloride. Thus, **1d** itself can be used as an useful template for parallel synthesis.

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Truncated diastereoselective Passerini reaction, a rapid construction of polysubstituted oxazole and peptides having an α-hydroxy-β-amino acid component

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Abstract—The reaction of aldehydes and ketones, including aliphatic and aromatic ones, with amides of α-isocyano-β-phenylpropionic acid in toluene in the presence of lithium bromide gives 2,4,5-trisubstituted oxazoles in good to excellent yield. Protected chiral α-amino aldehydes participate in this reaction to give, after hydrolysis of the oxazoles, norstatine-containing peptides in good overall yield. The nucleophilic addition of isonitriles to *N*,*N*-dibenzylphenylalanal is investigated for the first time and is found to be stereoselective leading predominantly to the *anti*-adduct (dr=9/1). On the other hand, the reaction between the *N*-Boc phenylalanal and isonitrile is non-stereoselective.

1. Introduction

The reaction of an isonitrile, an aldehyde and a carboxylic acid to provide an α-acyloxy amide was discovered by Passerini about 80 years ago.[1] Together with the Ugi reaction, it is among the most powerful multicomponent reactions and have found wide applications in the synthesis of large arrays of chemical species.[2] Recently, a sequence involving Passerini reaction followed by an intramolecular *O* to *N*-acyl migration has been developed by the group of Banfi[3] and Semple,[4] respectively, for the rapid atom-economy synthesis of enzyme inhibitors.[5] Lewis acid-mediated two-component variants leading to α-hydroxycarboxylic amides has been described by Seebach[6] and more recently, an enantioselective version has been uncovered by Denmark and Fan.[7] Being interested in the development of novel multicomponent synthesis of heterocycles, we have described a three-component synthesis of 5-aminooxazoles by condensation of aldehydes, amines and α-isocyano amides[8] and its subsequent transformation to a variety of polyheterocycles[9,10] and macrocycles.[11] Ganem and co-workers subsequently reported a Lewis acid promoted condensation between aldehydes and α-isocyano amides for the synthesis of polysubstituted 5-aminooxazoles.[12] As a continuation of our work in this field, we report herein a synthesis of 2,4,5-trisubstituted oxazoles (**1**) by a truncated Passerini reaction between aldehydes and α-alkyl-α-isocyano amides under mild conditions[13] and its application in the synthesis of peptides having a β-amino-α-hydroxy acid fragment (Fig. 1). The β-amino-α-hydroxy acid (norstatine) is the essential moiety of a large number of well-known natural or synthetic compounds that are endowed with powerful biological activities. Anticancer drugs such as paclitaxel and

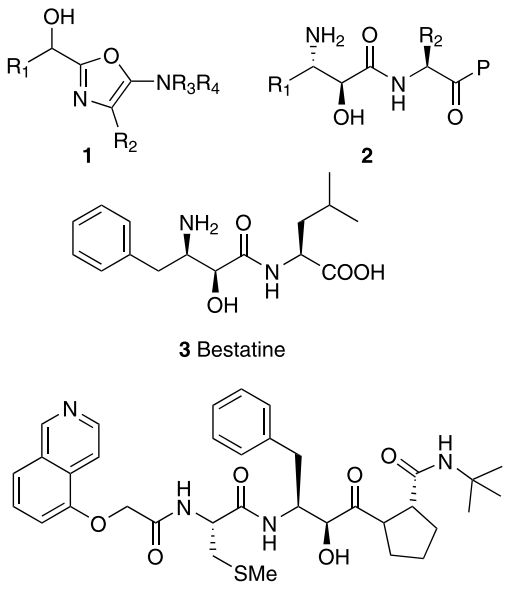

Figure 1.

Keywords: Diastereoselectivity; *N*,*N*-Dibenzyl aminoaldehyde; α-Hydroxy-β-amino acid; Multicomponent reaction; Oxazole; Passerini reaction.

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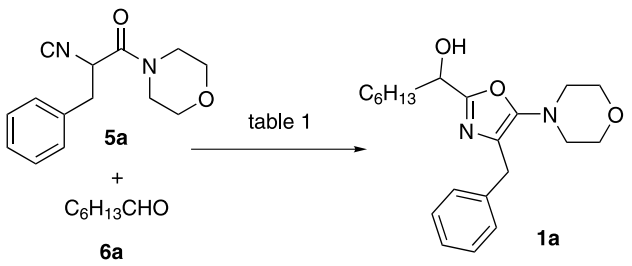
taxotère,[14] the potent aminopeptidase B inhibitor bestatine (**3**)[15] and potent HIV protease inhibitor (**4**)[16] are notable examples.

The reaction between α-isocyano β-phenyl propionamide (**5**) and heptanal (**6**) was investigated under different set of conditions following our previous work (Scheme 1). Table 1 summarized the results of reaction optimization under different conditions varying the solvent, the temperature and additives (weak Brønsted acids and weak Lewis acid). As can be seen, no reaction occurred in MeOH (entry 1) and toluene (entry 4) in the absence of promoters. However, lithium bromide (LiBr),[17] ammonium chloride (NH_4Cl)[18] and camphorsulphonic acid (CSA),[19] were all able to assist this transformation leading to the oxazole in good to excellent yields. Interestingly, in the presence of these promoters the condensation reaction took place in both polar protic solvent (MeOH) and non-polar aprotic solvent (toluene). The optimum conditions consist of heating the isocyanide (**5a**) and heptanal (**6a**) in toluene (70 °C) in the presence of 1 equiv. of LiBr. Under these conditions, the desired oxazole **1a** was isolated in 89% yield (entry 5). It is worthy noting that LiBr and NH_4Cl are sparsely soluble in toluene, so the reaction is in fact catalytic in nature.



Scheme 1.

Table 1. Screening of reaction conditions for the synthesis of **1a**

Entry	Solvent	Additive	Temperature (°C)	Yield (%)[a]
1	MeOH	—	55	0
2	MeOH	LiBr[b]	55	86
3	MeOH	NH_4Cl[b]	55	30
4	Toluene	—	70	0
5	Toluene	LiBr[b]	70	89
6	Toluene	NH_4Cl[b]	70	68
7	Toluene	CSA[c]	70	50

[a] Isolated yield.
[b] 1 equiv.
[c] CSA=camphorsulphonic acid, 0.1 equiv.

The generality of this transformation was demonstrated by applying the procedure to various aldehydes and α-alkyl α-isocyanoacetamides. Figure 2 lists 2-hydroxyalkyl-5-amino oxazoles synthesized by this new protocol. Aliphatic carbonyl compounds, including linear (heptanal), α-branched aldehydes (isobutyraldehyde) and activated aldehydes or ketones such as ethyl glyoxylate and keto malonate participate in this transformation to give the corresponding adducts. Aromatic aldehydes with electron withdrawing group or moderate electron donating group react smoothly leading to the oxazoles (**1g** to **1k**). However, 4-methoxybenzaldehyde failed to produce the corresponding oxazole, presumably because of its lower electrophilicity and/or the low stability of the resulting benzyl alcohol. The amine part of the α-isocyano-β-phenyl-propionamide influenced the reaction efficiency as well as the stability of adducts. Thus, piperidine-containing oxazoles are less stable than the morpholine derivatives (**1a** vs. **1b**, and **1h** vs. **1i**). In fact, it is rather difficult to obtain analytically pure **1b** and **1i** due to their low stability that partly explained the decreased yield of oxazoles **1b** and **1i**.

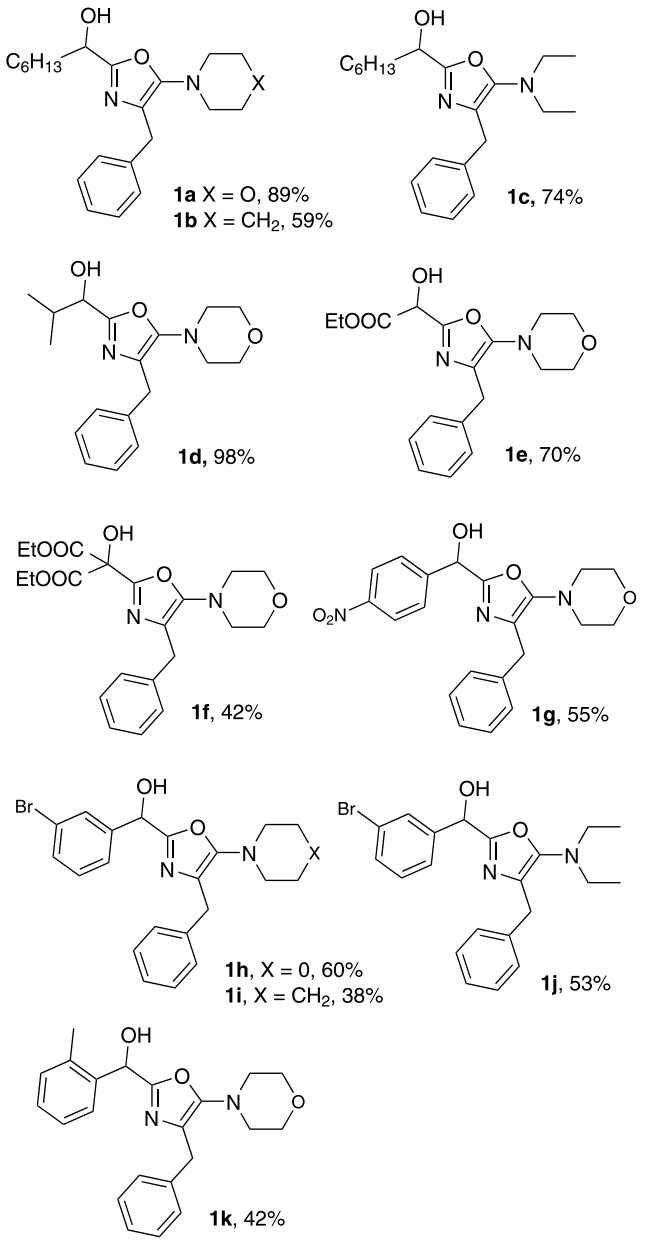
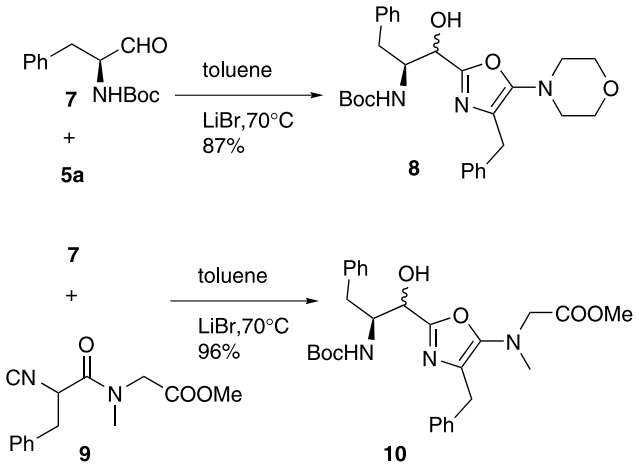


Figure 2.

It is important to note that it is essential to use the α-alkyl α-isocyanoacetamide since the reaction of heptanal and isocyanoacetate under identical conditions provided a complex reaction mixture.

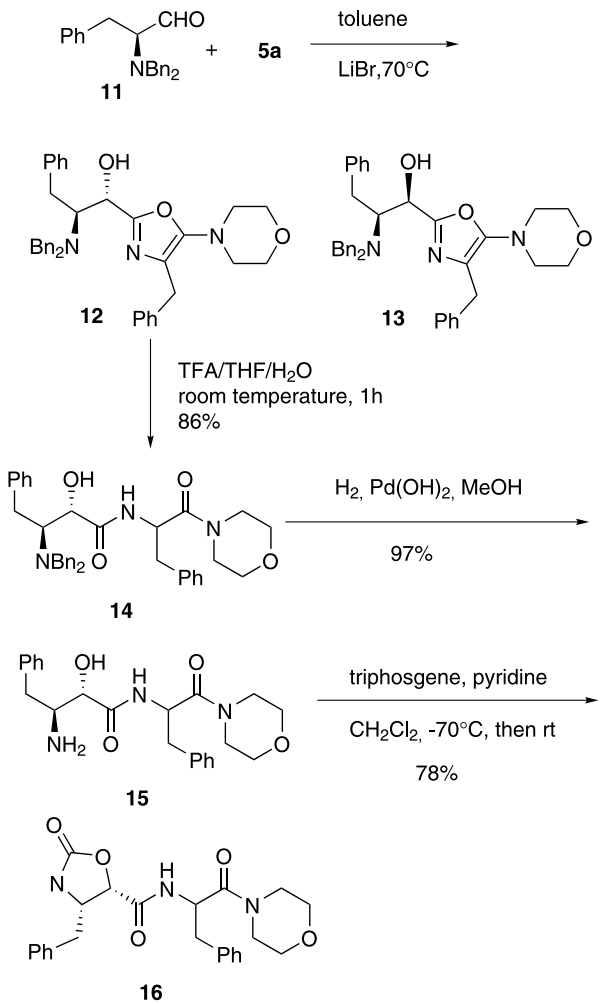
Synthesis of non-proteinogenic β-amino-α-hydroxy acids (norstatines),[20] followed by peptide coupling is the conventional way to prepare the peptide of general structure

2 (Fig. 1). Since 5-aminooxazole can be hydrolyzed to the acetamido amide under mild acidic conditions,[21] a two-step synthesis of norstatine-containing peptides can thus be envisaged starting from chiral non-racemic amino aldehydes. Indeed, the reaction of L-*N*-Boc-phenylalanal **7** with **5a** and dipeptidic isocyanide **9**[22] provided the corresponding oxazoles **8** and **10** in 87 and 96% yields, respectively. Unfortunately, the diastereoselectivity of this transformation was unacceptably low (dr=3/2). The chirality of α-isocyano amide (**5a**) has no influence on the diastereoselectivity since both (L) and racemic form provided similar results (Scheme 2).



Scheme 2.

The low selectivity in the formation of compounds **8** and **10** was not unexpected since the Passerini reaction involving chiral carbonyl compounds produce generally low to moderate diastereoselectivity, due to the low steric requirement of isocyano group. Recent elegant work from Marcaccini, Torroba[23] and Lamberth[24] nevertheless illustrated that excellent diastereoselectivity could be achieved if appropriate chiral starting materials were used. In light of Reetz's original contributions[25] and our own experiences on the diastereoselective transformation of *N*,*N*-dibenzylamino aldehyde,[26] the *N*,*N*-dibenzyl phenylalanal **11** was next examined. To our delight, the reaction of **5a** and **11** is much more stereoselective leading to the formation of two diastereomeric amino alcohols in a ratio of 9:1 (determined from the ^{1}H NMR spectra of the crude reaction mixture) and the major stereomer **12** was isolated in 64% yield. Hydrolysis of **12** under acidic conditions (THF–H_2O, TFA, room temperature) proceeded smoothly to provide the dipeptide **14** in 86% yield. The protonation of the C-4 carbon was non-stereoselective leading to the formation of dipeptide as a mixture of two separable diastereomers. Both diastereomers (**14a** and **14b**) were transformed to the corresponding oxazolidinone (**16**) in order to determine the relative stereochemistry of the amino alcohol (Scheme 3). Thus, hydrogenolysis of **14** under standard conditions [$Pd(OH)_2$, H_2, 1 atm, MeOH] provided the corresponding amino alcohol **15** which was reacted with triphosgene in the presence of pyridine to provide the oxazolidinone in 78% yield. The coupling constant (J_{Ha-Hb}=8.5 Hz) indicated a *cis* relation for these two protons and hence the *anti* stereochemistry of the amino alcohol in compound **12**. Nucleophilic addition to *N*,*N*-



Scheme 3.

dibenzylamino aldehydes leading to *anti*-adducts is well-known[25] and can be explained by the usual Felkin–Anh model (Fig. 3).[27]

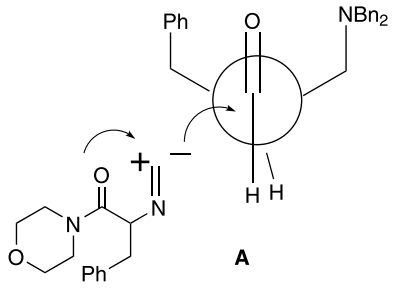


Figure 3.

In summary, we have developed a new synthesis of 2,4,5-trisubstituted oxazole by reaction of aldehyde with peptidic isocyanide. Using *N*,*N*-dibenzylamino phenylalanal, a highly diastereoselective Passerini reaction occurred to provide, after acidic hydrolysis of oxazole, the phenylnorstatine-containing dipeptide. To the best of our knowledge, this is the first example in which *N*,*N*-dibenzylamino aldehyde was used as chiral carbonyl input in the Passerini reaction. We expect the further application of the readily

available *N*,*N*-dibenzylamino aldehydes in the Passerini as well as in the Ugi type multicomponent reactions.

2. Experimental

2.1. Preparation of isonitrile 5a and 9

These two isonitriles were obtained by dehydration of the corresponding *N*-formyl derivatives.[22] Typical procedure: A stirred solution of morpholinyl amide of *N*-formyl phenylalanine (10 mmol) and triethylamine (50 mmol) in 50 mL of dry dichloromethane was cooled to −20 to −30°C. Phosphorus oxychloride (15 mmol) was added dropwise and the reaction mixture was stirred for 2 h at −20 to −30°C. An aqueous solution of sodium bicarbonate was introduced dropwise so that the temperature of mixture was maintained at −20 to −30°C. The mixture was stirred for 0.5 h and raised to room temperature. The aqueous layer was separated and extracted with dichloromethane. The organic extracts were combined, washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel to provide the isocyanide **5a**.

2.1.1. Compound 5a. Yield: 95%; eluant: Hept/EtOAc=2/1; white solid, mp 79–81°C; IR ($CHCl_3$) ν 2928, 2863, 2142, 1668, 1496, 1456, 1116 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 3.13–3.78 (m, 10H), 4.55 (t, 1H, J=7.3 Hz), 7.22–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ 39.1, 42.9, 46.2, 55.0, 65.9, 66.4, 127.7, 128.8 (2CH), 129.4 (2CH), 135.0, 159.8, 163.5; MS (EI): *m*/*z* 244.

2.1.2. Compound 9. Yield 98% (eluant: EtOAc/Hept=1/5); IR ($CHCl_3$, cm^{-1}) ν 3009, 2142, 1751, 1677, 1497, 1456, 1439, 1407, 1366, 1238, 1183, 1121, 1080, 1032; $[\alpha]_D$=−8.3 (c=0.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, ppm), two rotamers (4/1 ratios) δ 3.08 (3.02) (s, 3H), 3.15 (dd, J=8.7, 14.0 Hz, 1H), 3.28 (dd, J=5.3, 14.0 Hz, 1H), 3.76 (s, 3H), 4.02 (3.90) [d, J=17.3 (17.2) Hz, 1H], 4.26 (4.09) (d, J=17.3 (17.2) Hz, 1H), 4.62 (4.39) [d, J=5.5 (5.5), 8.7 (8.8) Hz, 1H], 7.20–7.36 (5H, m); ^{13}C NMR (62.5 MHz, $CDCl_3$, ppm), two rotamers (4/1 ratios) δ 35.90, 36.75, 38.68, 39.03, 50.14, 51.22, 52.39, 55.80, 127.7, 128.8, 129.5, 135.2, 160.0, 165.8, 168.9; MS (EI) *m*/*z* 260, 233, 201, 174. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.62; H, 6.15; N, 10.77. Found: C, 64.77; H, 6.07; N, 10.74.

2.2. Typical procedure for the truncated Passerini reaction, synthesis of compound 1a

To a solution of heptanal (**6a**, 0.20 mmol, 26.9 μL) and α-isocyano β-phenyl propionamide (**5a**) (0.15 mmol, 37.6 mg) in dry toluene (0.30 mL) was added lithium bromide (0.15 mmol, 13.4 mg.). The reaction mixture is stirred at 60 °C for 4 h. After the disappearance of isonitrile, the reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate. The combined organic phase was washed with brine, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The crude reaction mixture was purified by flash chromatograph (AcOEt/Hept 1/2) to give the corresponding oxazole **1a** (49.3 mg, 89% yield). R_f=0.39 (eluant: AcOEt/Hept=2/3); IR ($CHCl_3$) ν 3416, 2929, 2860, 1737, 1665, 1454, 1376, 1264, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.87 (m, 3H), 1.25 (m, 8H), 1.73–1.86 (m, 2H), 2.94 (m, 4H), 3.70 (m, 4H), 3.80 (s, 2H), 4.61 (br t, 1H, J=6.2 Hz), 7.18–7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.6, 25.1, 28.9, 31.4, 31.7, 51.1, 66.9, 71.9, 124.7, 128.3–128.4, 139.3, 151.9, 160.7; MS (ESI) *m*/*z* 359 (M+H), 381 (M+Na); HRMS (ESI) *m*/*z* calculated for $C_{21}H_{30}N_2O_3$+Na: 381.21333, found 381.2132.

Compounds **1b**–**1k**, **8**, **10** and **12** were prepared under identical conditions.

2.2.1. Compound 1b. R_f=0.68 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3411, 2930, 2860, 1723, 1631, 1496, 1453, 1269, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.87 (m, 3H), 1.27 (m, 8H), 1.52 (m, 2H), 1.61 (m, 4H), 1.83 (m, 2H), 2.94 (m, 4H), 3.78 (s, 2H), 4.60 (br t, 1H, J=5.8 Hz), 7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.5, 22.6, 23.9, 25.9, 28.9, 31.4, 31.7, 52.2, 71.7, 123.4, 128.5, 139.7, 153.5, 159.9; MS (ESI) *m*/*z* 357 (M+H), 379 (M+Na).

2.2.2. Compound 1c. R_f=0.70 (eluant: AcOEt/Hept=1/1); ^1H NMR (250 MHz, $CDCl_3$, 293 K) δ 0.87 (m, 3H), 0.98 (t, 6H, J=7.3 Hz), 1.26 (m, 8H), 1.83 (m, 2H), 2.71 (d, 1H, J=5.5 Hz, OH), 2.95 (q, 4H, J=7.3 Hz), 3.77 (s, 2H), 4.62 (m, 1H), 7.25 (m, 5H); MS (ESI) *m*/*z* 367 (M+Na), 383 (M+K).

2.2.3. Compound 1d. R_f=0.43 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3411, 2964, 2927, 2856, 1638, 1454, 1262, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.92 (d, 3H, J=6.7 Hz), 0.96 (d, 3H, J=6.7 Hz), 2.11 (m, 1H), 2.95 (m, 4H), 3.72 (m, 4H), 3.82 (s, 2H), 4.39 (d, 1H, J=6.7 Hz), 7.19–7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 18.4, 31.8, 33.5, 51.2, 66.9, 73.05, 124.7, 126.3, 128.5, 139.4, 152.1, 160.1; MS (ESI) *m*/*z* 317 (M+H), 339 (M+Na).; HRMS (ESI) *m*/*z* calculated for $C_{18}H_{24}N_2O_3$+Na: 339.1664, found 339.1665.

2.2.4. Compound 1e. R_f=0.50 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3519, 2862, 2142, 1743, 1664, 1453, 1265, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.26 (t, 3H, J=7.3 Hz), 2.97 (m, 4H), 3.72 (m, 4H), 3.82 (s, 2H), 4.31 (m, 2H), 5.16 (s, 1H), 7.23 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 31.6, 50.7, 62.6, 66.6, 67.1, 125.1, 127.6, 128.3, 129.3, 139.1, 154.2, 163.4, 169.9; MS (ESI) *m*/*z* 347 (M+H), 369 (M+Na), 385 (M+K); HRMS (ESI) *m*/*z* calculated for $C_{18}H_{22}N_2O_5$+Na: 369.1426, found 369.1381.

2.2.5. Compound 1f. R_f=0.49 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3494, 2987, 1747, 1660, 1453, 1264, 1115 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 293 K) δ 1.29 (t, 6H, J=7.0 Hz), 2.95 (m, 4H), 3.71 (m, 4H), 3.83 (s, 2H), 4.36 (m, 4H), 7.24 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 31.8, 50.8, 63.5, 66.7, 125.1, 126.2, 128.3, 128.5, 139.2, 152.3, 153.0, 166.8; MS (ESI) *m*/*z* 419 (M+H), 441 (M+Na), 457 (M+K), 859 (2M+Na); HRMS (ESI) *m*/*z* calculated for $C_{21}H_{26}N_2O_7$+Na: 441.1638, found 441.1599.

2.2.6. Compound 1g. R_f=0.34 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3400, 2925, 2860, 1666, 1529, 1454, 1349, 1264, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.92 (m, 4H), 3.71 (m, 4H), 3.80 (s, 2H), 5.76 (s, 1H), 7.21 (m, 5H), 7.65 (d, 2H, J=8.8 Hz), 8.22 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.7, 50.9, 66.8, 69.0, 123.8, 124.6, 126.5, 127.4, 127.8, 128.5, 128.6, 128.9, 129.5, 139.0, 146.3, 147.8, 152.9, 157.9; MS (ESI) m/z 396 (M+H), 418 (M+Na); HRMS (ESI) m/z calculated for $C_{21}H_{21}N_3O_5$+Na: 418.1379, found 418.1398.

2.2.7. Compound 1h. R_f=0.45 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3391, 2968, 2921, 2861, 1664, 1453, 1263, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.92 (m, 4H), 3.69 (m, 4H), 3.80 (s, 2H), 5.63 (s, 1H), 7.23 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.6, 51.0, 66.7, 69.2, 122.6, 124.4, 125.4, 126.3, 128.5, 129.4, 129.7, 131.3, 139.3, 141.7, 152.6, 158.6; MS (ESI) m/z 429, 431 (M+H), 451, 453 (M+Na), 467, 469 (M+K); HRMS (ESI) m/z calculated for $C_{21}H_{21}N_2O_3Br$+Na: 451.0633 and 453.0613, found 451.0662 and 453.0630.

2.2.8. Compound 1i. IR ($CHCl_3$) ν 3403, 2942, 2858, 1631, 1453, 1271, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.50–1.60 (m, 6H), 2.90 (m, 4H), 3.77 (s, 2H), 5.60 (s, 1H), 7.19–7.29 (m, 6H), 7.32 (d, 1H, J=7.4 Hz), 7.41 (d, 1H, J=8.0 Hz), 7.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.9, 31.7, 52.0, 69.3, 122.6, 122.9, 125.2, 126.2, 128.5, 129.4, 129.7, 131.2, 139.5, 141.8, 154.2, 157.8; MS (ESI) m/z 427, 429 (M+H); 449, 451 (M+Na); HRMS (ESI) m/z calculated for $C_{22}H_{23}N_2O_2Br$+Na: 449.0796 and 451.0775, found 449.0802 and 451.0791.

2.2.9. Compound 1j. R_f=0.67 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3417, 2932, 1728, 1633, 1455, 1383, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.94 (t, 6H, J=7.3 Hz), 2.92 (q, 4H, J=7.3 Hz), 3.77 (s, 2H), 5.63 (br s, 1H), 7.19–7.27 (m, 6H), 7.32 (d, 1H, J=7.3 Hz), 7.42 (dd, 1H, J=1.7, 7.3 Hz), 7.58 (d, 1H, J=1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.2, 31.4, 47.8, 69.5, 122.6, 125.2, 126.1, 127.9, 128.3, 128.5, 128.6, 129.7, 129.9, 130.1, 131.3, 139.3, 141.9, 151.7, 159.0; MS (IE) m/z 414, 416 (M)+; HRMS (ESI) m/z calculated for $C_{21}H_{23}N_2O_2Br$+Na: 437.0841 and 439.0820, found 437.0864 and 439.0850.

2.2.10. Compound 1k. R_f=0.41 (eluant: AcOEt/Hept=1/1); IR ($CHCl_3$) ν 3404, 2967, 2922, 2861, 1636, 1495, 1453, 1263, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.39 (s, 3H), 2.89 (m, 4H), 3.69 (m, 4H), 3.81 (s, 2H), 5.90 (s, 1H), 7.19–7.27 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.1, 31.6, 51.0, 66.8, 67.5, 124.5, 126.2, 126.6, 128.4, 128.5, 129.1, 130.6, 130.8, 136.0, 137.7, 139.3, 146.3, 152.3, 159.1; MS (ESI) m/z 365 (M+H), 387 (M+Na), 403 (M+K); HRMS (ESI) m/z calculated for $C_{22}H_{24}N_2O_3$+Na: 387.1685, found 387.1664.

2.2.11. Compound 8a. R_f=0.41 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−1 ($CHCl_3$, c 1.9); IR ($CHCl_3$) ν 3439, 2927, 2862, 1705, 1495, 1454, 1368, 1162, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.38 (s, 9H), 2.76 (dd, 1H, J_1=6.3 and J_2=13.9 Hz), 2.78 (dd, 1H, J=6.3, 13.9 Hz), 2.93 (m, 4H), 3.72 (m, 4H), 3.79 (s, 2H), 4.32 (m, 1H), 4.67 (d, 1H, J=2.9 Hz), 5.07 (br d, 1H, J=9.0 Hz), 7.11–7.35 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 29.4, 29.7, 31.7, 50.9, 53.8, 66.8, 79.7, 126.4, 128.4, 129.0, 137.5, 139.3, 152.3, 157.5; MS (ESI) m/z 516 (M+Na).

2.2.12. Compound 8b. R_f=0.45 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−6 ($CHCl_3$, c 1.4); IR ($CHCl_3$) ν 3439, 2927, 2862, 1705, 1495, 1454, 1368, 1162, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.30 (s, 9H), 2.92 (m, 6H), 3.69 (m, 4H), 3.74 (d, 1H, J=15.4 Hz), 3.76 (d, 1H, J=15.4 Hz), 4.23 (m, 1H), 4.50 (d, 1H, J=2.9 Hz), 4.91 (br d, 1H, J=10.3 Hz), 7.14–7.28 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 29.4, 29.7, 31.7, 50.9, 53.8, 66.8, 79.7, 126.4, 128.4, 129.0, 137.5, 139.3, 152.3, 157.5; MS (ESI) m/z 494 (M+H), 516 (M+Na); HRMS (ESI) m/z calculated for $C_{28}H_{35}N_3O_5$+Na: 516.2430, found 516.2429.

2.2.13. Compound 10a. R_f=0.45 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−3 ($CHCl_3$, c 0.9); IR ($CHCl_3$) ν 3434, 2931, 1710, 1497, 1368, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.30 (s, 9H), 2.83 (s, 3H), 2.91 (d, 2H, J=8.1 Hz), 3.67 (s, 3H), 3.68 (s, 2H), 3.72 (d, 1H, J=15.4 Hz), 3.80 (d, 1H, J=15.4 Hz), 4.20 (m, 1H), 4.47 (d, 1H, J=2.9 Hz), 4.93 (br d, 1H, J=9.6 Hz), 7.16–7.27 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 29.7, 31.4, 37.7, 40.9, 51.8, 55.7, 68.1, 79.2, 126.1, 126.5, 128.4, 128.5, 129.4, 137.9, 139.4, 152.3, 157.7, 170.6; MS (ESI) m/z 510 (M+H), 532 (M+Na), 548 (M+K).

2.2.14. Compound 10b. R_f=0.42, (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−7 ($CHCl_3$, c 0.8); IR ($CHCl_3$) ν 3434, 2931, 1710, 1497, 1368, 1164 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 1.37 (s, 9H), 2.70 (dd, 1H, J=6.4, 13.8 Hz), 2.76 (dd, 1H, J=6.4, 13.8 Hz), 2.86 (s, 3H), 3.69 (s, 7H), 3.82 (s, 2H), 4.30 (m, 1H), 4.64 (d, 1H, J=2.9 Hz), 5.12 (br d, 1H, J=9.6 Hz), 7.14–7.25 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 29.7, 31.4, 37.7, 40.9, 51.8, 55.7, 68.1, 79.2, 126.1, 126.5, 128.4, 128.5, 129.4, 137.9, 139.4, 152.3, 157.7, 170.6; MS (IE) m/z 509 $(M)^+$.

2.2.15. Compound 12. R_f=0.65 (eluant: AcOEt/Hept=1/1); $[\alpha]_D$=−13 ($CHCl_3$, c 0.7); IR ($CHCl_3$) ν 3400, 2927, 1495, 1454, 1114 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.75 (m, 4H), 2.86–2.93 (dd, 1H, J=7.7, 13.7 Hz), 2.98–3.05 (dd, 1H, J=6.0, 13.7 Hz), 3.37–3.43 (m, 1H), 3.53 (d, 2H, J=13.7 Hz), 3.59 (d, 2H, J=13.7 Hz), 3.64 (m, 4H), 3.69 (d, 1H, J=15.4 Hz), 3.75 (d, 1H, J=15.4 Hz), 4.71 (br d, 1H, J=3.8 Hz), 7.15–7.26 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 31.7, 51.0, 54.7, 63.4, 66.8, 125.2, 126.0, 126.1, 127.1, 127.4, 128.3, 128.33, 128.5, 128.6, 128.9, 129.1, 129.13, 129.4, 139.3, 151.9, 158.9. MS (ESI) m/z 596 (M+Na); HRMS (ESI) m/z calculated for $C_{37}H_{39}N_3O_3$+Na: 596.2889, found 596.2871.

2.2.16. Compound 13. R_f=0.67 (eluant: AcOEt/Hept 1:1) $[\alpha]_D$=+11 ($CHCl_3$, c 0.2); IR ($CHCl_3$) ν 3401, 2925, 1497, 1454, 1115 $cm^{-1;}$ ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.56 (dd, 1H, J=7.1, 14.3 Hz), 2.66 (m, 4H), 3.08 (dd, 1H, J=5.5, 14.3 Hz), 3.42–3.48 (m, 1H), 3.47 (d, 2H, J=13.2 Hz), 3.59 (m, 4H), 3.68 (s, 2H), 3.93 (d, 2H, J=13.2 Hz), 4.57 (d, 1H, J=9.3 Hz), 6.98–7.34 (m, 20H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 31.7, 51.0, 54.7, 63.4, 66.8, 125.2, 126.0, 126.1, 127.1, 127.4, 128.3, 128.33,

128.5, 128.6, 128.9, 129.1, 129.13, 129.4, 139.3, 151.9, 158.9; MS (ESI) *m/z* 574 (M+H), 596 (M+Na); HRMS (ESI) *m/z* calculated for $C_{37}H_{39}N_3O_3$ $(M+H)^+$ 574.3070, found 574.3074.

2.2.17. Compound 14. To the solution of oxazole **12** (72 mg, 0.13 mmol) in THF (0.3 mL) and water (0.3 mL), was added trifluoroacetic acid (0.3 mL). After being stirred at room temperature for 30 min, the reaction mixture was diluted with CH_2Cl_2, and washed with a saturated solution of $NaHCO_3$. The aqueous portion is extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was then purified on preparative TLC (eluant: AcOEt/methanol 10:0.1) to give **14** as a mixture of two separable diastereomers (1/1) in 86% yield.

*Diastereomer **14a***. R_f=0.17 (eluant: AcOEt/Hept 2/1); $[\alpha]_D$=−3 ($CHCl_3$, *c* 0.3); IR ($CHCl_3$) ν 3400, 2963, 1638, 1496, 1455, 1262, 1113, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.60–2.76 (m, 4H), 3.10–3.22 (m, 4H), 3.28–3.39 (m, 4H), 3.52 (m, 1H), 3.59 (d, 2H, *J*=13.7 Hz), 3.76 (d, 2H, *J*=13.7 Hz), 3.97 (br d, 1H, *J*=3.6 Hz), 4.97–5.05 (m, 1H), 7.07–7.10 (m, 1H), 7.19–7.34 (m, 20H), 7.74 (br d, 1H, *J*=8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.4, 40.2, 41.9, 45.7, 48.9, 53.4, 54.9, 63.7, 65.8, 66.1, 68.4, 126.2, 127.1, 127.5, 128.4, 128.5, 128.6, 128.7, 128.9, 129.1, 129.5, 129.6, 136.2, 138.2, 138.9, 139.5, 169.1, 172.7; MS (ESI) *m/z* 592 (M+H), 614 (M+Na), 630 (M+K); HRMS (ESI) *m/z* calculated for $C_{37}H_{41}N_3O_4$+H: 592.3175, found 592.3207.

*Diastereomer **14b***. R_f=0.42 (eluant: AcOEt/Hept 2/1); $[\alpha]_D$=−14 ($CHCl_3$, *c* 0.5); IR ($CHCl_3$) ν 3400, 2963, 1638, 1496, 1455, 1262, 1113, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.59–3.44 (m, 13H), 3.48 (d, 2H, *J*=13.8 Hz), 3.72 (d, 2H, *J*=13.8 Hz), 3.90 (d, 1H, *J*=3.6 Hz), 4.99 (td, 1H, *J*=5.0, 8.9 Hz), 7.16–7.34 (m, 20H), 7.76 (d, 1H, *J*=8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.3, 40.2, 41.9, 45.7, 48.9, 54.9, 63.8, 65.8, 66.1, 68.4, 126.2, 127.1, 127.5, 128.4, 128.6, 128.7, 128.9, 129.5, 129.6, 136.2, 138.9, 139.5, 169.1, 172.7; MS (ESI) *m/z* 592 (M+H), 614 (M+Na); HRMS (ESI) *m/z* calculated for $C_{37}H_{41}N_3O_4$+H: 592.3175, found 592.3212.

2.2.18. Compound 15. A solution of diastereomerically pure compound **14** (diastereomer **14a**, 191 mg, 0.32 mmol) in MeOH was stirred in the presence of palladium hydroxide under hydrogen pressure for 3 h. The reaction mixture was filtered through a Celite pad and washed with methanol. The resulting filtrate is evaporated under reduced pressure to give the desired free amino alcohol **15a** (140 mg, 97% yield): R_f=0.10 (eluant: AcOEt/Hept 4:1); $[\alpha]_D$=−1 ($CHCl_3$, *c* 0.6); IR ($CHCl_3$) ν 3392, 2928, 1638, 1518, 1445, 1268, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 293 K) δ 2.49 (dd, 1H, *J*=4.8, 14.4 Hz), 2.64 (dd, 1H, *J*=9.7, 14.4 Hz), 2.94 (dd, 1H, *J*=7.8, 13.3 Hz), 2.98 (dd, 1H, *J*=7.8, 13.3 Hz), 3.44–3.58 (m, 8H), 3.70 (m, 1H), 4.29 (br d, 1H, *J*=2.4 Hz), 5.04 (t, 1H, *J*=7.8 Hz), 7.18–7.36 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD) δ 34.3, 39.3, 43.7, 47.5, 51.0, 56.3, 67.3, 67.4, 71.9, 128.3, 128.5, 129.7, 130.0, 130.5, 130.7, 136.9, 137.5, 171.5, 172.3. MS (ESI) *m/z* 412 (M+H); HRMS (ESI) *m/z* calculated for $C_{23}H_{29}N_3O_4$+Na: 434.2056, found 434.2048.

The diastereomer **15b** was prepared from **14b** following the identical procedure.

Compound **15b**. R_f=0.14 (eluant: AcOEt/Hept 9:1); $[\alpha]_D$=−2 ($CHCl_3$, *c* 0.3); IR ($CHCl_3$) ν 3392, 2928, 1638, 1518, 1445, 1268, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 293 K) δ 2.78 (dd, 1H, *J*=8.5, 14.6 Hz), 2.94–3.08 (m, 5H), 3.17–3.23 (m, 2H), 3.43–3.61 (m, 4H), 3.78–3.80 (m, 1H), 4.31 (br d, 1H, *J*=2.4 Hz), 4.95 (m, 1H), 7.25–7.32 (m, 10H); ^{13}C NMR (75 MHz, CD_3OD) δ 34.6, 39.4, 43.7, 47.4, 51.3, 56.8, 67.2, 67.4, 71.6, 128.3, 128.4, 129.8, 129.9, 130.1, 130.5, 130.7, 136.9, 137.4, 171.4, 172.2; MS (ESI) *m/z* 412 (M+H); HRMS (ESI) *m/z* calculated for $C_{23}H_{29}N_3O_4$+H: 412.2236, found 412.2248.

2.2.19. Compound 16. A solution of trisphosgene (19.7 mg, 0.07 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise to a solution of pyridine (65 μL, 0.79 mmol) and the amino alcohol **15a** (54.6 mg, 0.13 mmol) in CH_2Cl_2 (0.45 mL) cooled to −70 °C. Once addition was completed, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The resultant homogenous solution was quenched with saturated ammonium chloride and the aqueous portion was separated and extracted with CH_2Cl_2. The organic extract were washed with 1 N HCl, saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified on preparative TLC (eluant: AcOEt/methanol 10:1) to give the desired oxazolidinone **16a** (45 mg, 78% yield): R_f=0.60 (eluant: AcOEt/methanol 10/1); $[\alpha]_D$=−100 ($CHCl_3$, *c* 0.8); IR ($CHCl_3$) ν 3399, 2927, 1777, 1678, 1643, 1521, 1445, 1267, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.11 (dd, 1H, *J*=12.7, 12.8 Hz), 2.81 (dd, 1H, *J*=12.8, 2.8 Hz), 2.97–3.34 (m, 6H), 3.37–3.63 (m, 4H), 4.11 (ddd, 1H, *J*=2.8, 8.4, 12.7 Hz), 5.02 (d, 1H, *J*=8.4 Hz), 5.20–5.26 (m, 1H), 7.08–7.35 (m, 10H), 7.56 (d, 1H, *J*=8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 36.5, 39.8, 42.4, 46.0, 49.2, 55.5, 66.1, 66.5, 127.2, 127.4, 128.3, 128.7, 128.8, 129.1, 129.3, 129.5, 129.6, 135.7, 136.1, 165.8, 169.1; MS (ESI) *m/z* 460 (M+Na). The diastereomer **16b** was prepared from **15b** following the identical procedure.

Compound **16b**. R_f=0.61 (eluant: AcOEt/methanol 10/1); $[\alpha]_D$=−123 ($CHCl_3$, *c* 0.6); IR ($CHCl_3$) ν 3399, 2927, 1777, 1678, 1643, 1521, 1445, 1267, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K) δ 2.40 (dd, 1H, *J*=11.8, 13.2 Hz), 2.91–3.08 (m, 7H), 3.33–3.55 (m, 4H), 4.24 (ddd, 1H, *J*=2.9, 8.5, 11.8 Hz), 5.05 (d, 1H, *J*=8.5 Hz), 5.13 (q, 1H, *J*=8.0 Hz), 7.18–7.32 (m, 10H), 7.70 (d, 1H, *J*=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.8, 39.3, 42.4, 46.1, 49.5, 55.7, 66.1, 66.5, 127.3, 127.5, 128.8, 129.1, 129.5, 135.7, 136.2, 156.6, 166.1, 169.3; MS (ESI) *m/z* 460 (M+Na); HRMS (ESI) *m/z* calculated for $C_{24}H_{27}N_3O_5$+Na: 460.1848, found 460.1848.

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Synthesis of novel triazolopyridylboronic acids and esters. Study of potential application to Suzuki-type reactions

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Abstract—This paper describes a general method for the synthesis of novel [1,2,3]triazolo[1,5-*a*]pyridylboronic acids and esters, and the first results on Suzuki cross-coupling reactions with these new compounds and [1,2,3]triazolo[5,1-*a*]isoquinolylboronic acid, reacting with a variety of aryl halides as a route to 7-aryltriazolopyridines and 5-aryltriazoloisoquinolines.

1. Introduction

During our research on the chemistry of [1,2,3]triazolo[1,5-*a*]pyridines **1** and [1,2,3]triazolo[5,1-*a*]isoquinoline **2**, we discovered a facile route to new bistriazolopyridines and related compounds, which are potential helicating ligands, using compounds **1** and **2** as building blocks.[1–3] The interest of this type of compounds,[4] led us to attempt to widen the scope of their synthesis by alternative routes. The Suzuki reaction would be applicable to the preparation of heteroaryltriazolopyridines and heteroaryltriazoloisoquinolines, which are also potentially interesting in the field of new selective inhibitors of cyclooxygenase 2. In contrast of the many examples of Suzuki coupling reactions between heterocyclic halides and phenyl boronic acids that have appeared in the literature over the past two decades,[5,6] the corresponding reactions involving heterocyclic boronic acids or esters are noticeably fewer,[7] nevertheless interest in heterocyclic boronic derivatives continues to grow and we wish to report here the synthesis of novel [1,2,3]triazolo[1,5-*a*]pyridylboronic acids **3a–c**, esters **4a–c** and **5**, and the first results on Suzuki cross-coupling reactions with these new compounds and [1,2,3]triazolo[5,1-*a*]isoquinolyl boronic acid **6** reacting with a variety of aryl halides.

2. Results and discussion

The starting materials **1a–c**, and **2**, were prepared by procedures described in the literature.[8,2,9] We used the classical preparation of boronic acids which requires the reaction of an organolithium intermediate, generated by deprotonation, with a trialkylborate.[10–12] The corresponding lithium derivatives **7** and **8** were formed in toluene at −40 °C with *n*-BuLi,[13] followed by reaction with triisopropyl borate. The reaction mixture was quenched with slow addition of 5% aqueous NaOH solution and the resulting aqueous layer neutralized by careful addition of concentrated HCl. The new triazolopyridyl boronic acids **3a–c** were stable yellow solids, the triazoloisoquinolyl boronic acid **6** was a stable white solid.[3] All acids were insoluble in usual organic solvents, were relatively easy to handle and purify, could be analyzed by ESI-MS, and were obtained with yields from 40 to 78%. The pinacol esters **4a–c** were obtained using similar conditions to those described previously to obtain pinacol esters from the halopyridyl boronic acids, in an one pot procedure.[14] Compounds **4a–c** are stable and were obtained in high yield. The borolane **5b** was prepared by the procedure described by some of us,[15] from the corresponding boronic acid by reaction with N-methyldiethanolamine in excellent yield (Scheme 1).

The boronic acids were directly subjected to modified Suzuki cross-coupling conditions, (DME/aqueous K_2CO_3/$Pd(PPh_3)_4$/80 °C),[11,16] with 4-iodoanisole. The triazolopyridyl derivatives **3a**,**b** gave protodeboronation as the main result and triazolopyridines **1a**,**b** were recovered from the reaction mixture in almost quantitative yield (Scheme 2).

Keywords: Triazolopyridines; Triazoloisoquinolines; Boronic acids and esters; Suzuki cross-coupling reaction.
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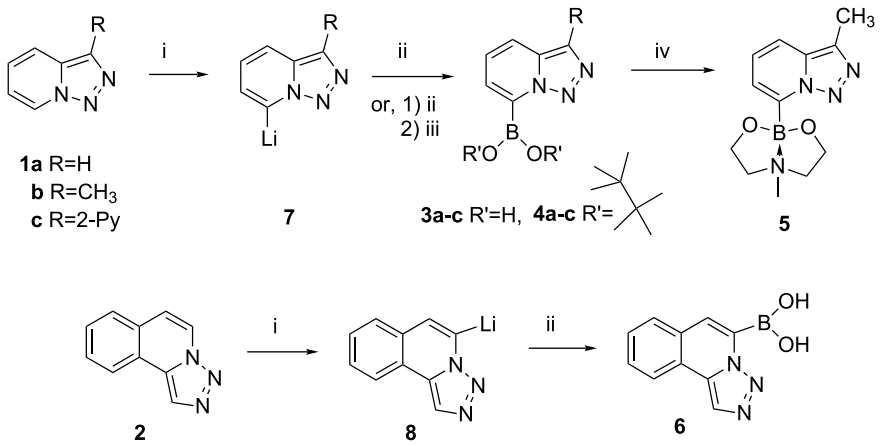
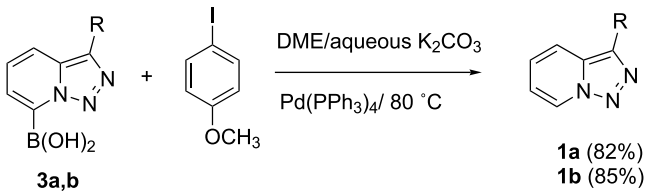


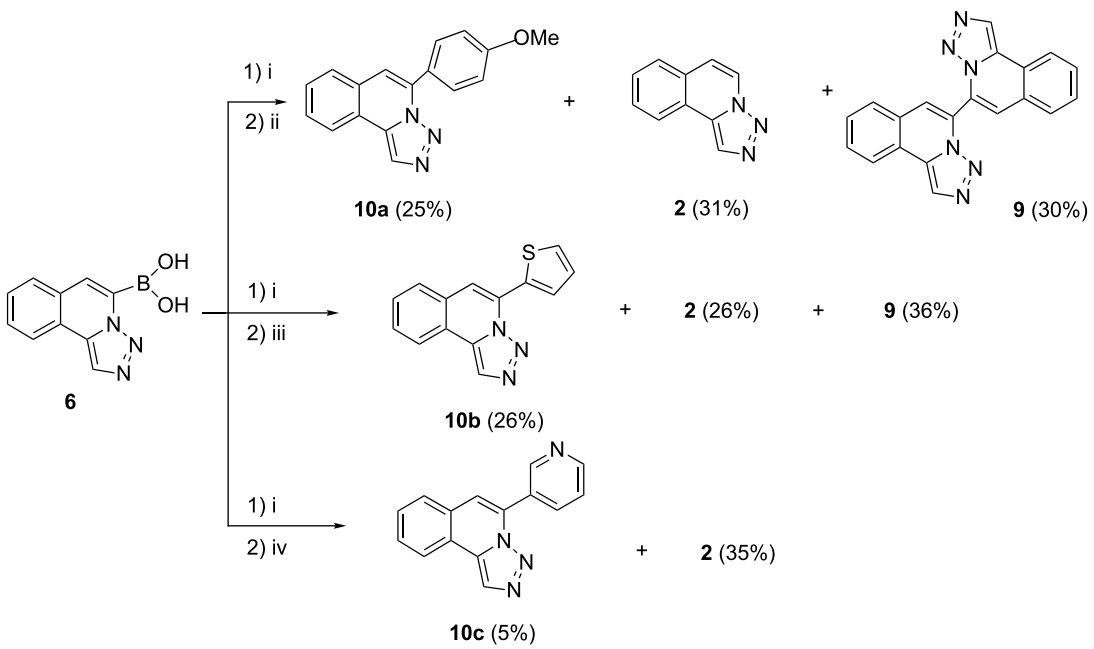
Scheme 1. i, *n*-BuLi/toluene; ii, $B(OiPr)_3$; iii, pinacol; iv, $MgSO_4$/N-methyldiethanolamine (from **3b**).



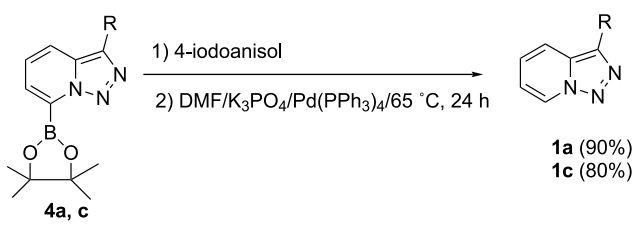
Scheme 2.

The triazoloisoquinoline boronic acid **6** gave a mixture of three compounds that were characterized as triazoloisoquinoline **2** (31%), bistriazoloisoquinoline **9** (30%),[3] and the heterobiaryl derivative **10a** (25%) (Scheme 3).

The pinacol esters **4a** and **4c** gave only protodeboronation (Scheme 4), nevertheless the pinacol ester **4b** under standard Suzuki-type conditions, (DMF/K_3PO_4/$Pd(PPh_3)_4$/65 °C),[14] gave better results furnishing furthermore protodeboronation, the heterobiaryl derivative **11a** but



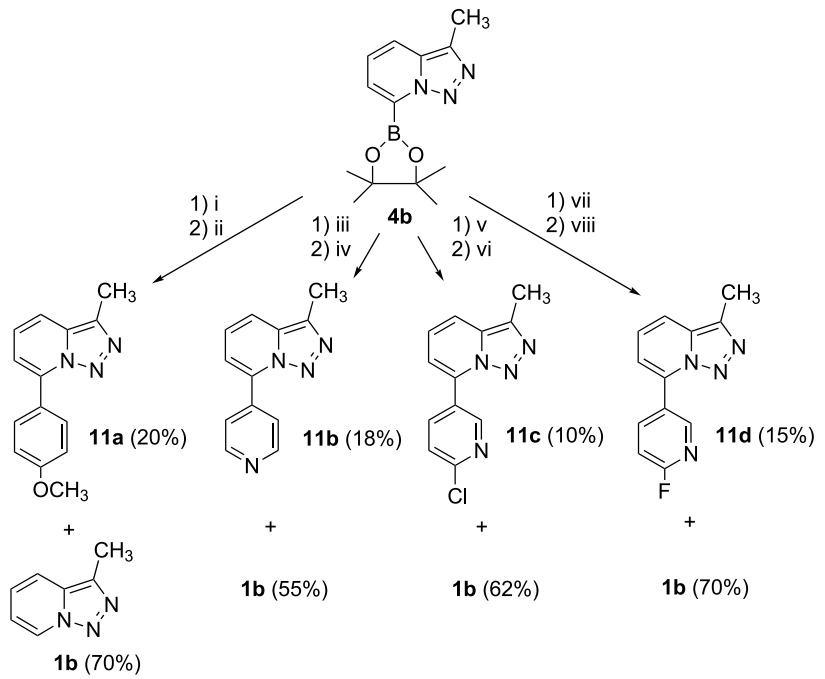
Scheme 3. i, $DME/NaHCO_3/H_2O$, 45 °C, 15 m; ii, 4-iodoanisol/$Pd(PPh_3)_4$/DME/reflux, 6 h; iii, 2-bromothiophene/$Pd(PPh_3)_4$/DME/reflux, 6 h; iv, 3-bromopyridine/$Pd(PPh_3)_4$/DME/reflux, 6 h.



Scheme 4.

only in low yield (20%) (Scheme 5). Such different reactivity is probably due to the better solubility and stability of the compound **4b**.

We followed the research with the boronic ester **4b** and the boronic acid **6**, that underwent Suzuki couplings. We did several attempts to improve the results modifying the reaction conditions, a number of bases (K_2CO_3, Na_3PO_4, K_3PO_4, $NaHCO_3$, KOH, $Ba(OH)_2{\cdot}8H_2O$), solvents



Scheme 5. i, 4-iodoanisol/Pd(PPh$_3$)$_4$/DMF; ii, K$_3$PO$_4$/H$_2$O, 70 °C, 16 h; iii, 4-iodopyridine/Pd(PPh$_3$)$_4$/dioxane; iv, Ba(OH)$_2$.8H$_2$O/H$_2$O/90–100 °C, 20 h; v, 2-chloro-5-iodopyridine/Pd(PPh$_3$)$_4$/dioxane; vi, Ba(OH)$_2$.8H$_2$O/H$_2$O/80–100 °C, 24 h; vii, 5-bromo-2-fluorpyridine/Pd(PPh$_3$)$_4$/dioxane; viii, Ba(OH)$_2$.8H$_2$O/H$_2$O/50–60°C, 72 h.

(DME/H$_2$O, DMF/H$_2$O, toluene, acetone, dioxane), catalysts (Pd(PPh$_3$)$_4$ purchased from commercial sources: Aldrich; Lancaster, Pd/C 10%), and co-reagents (2-bromopyridine, 2-bromothiophene, 3-bromopyridine, 4-iodopyridine, 2-chloro-5-iodopyridine, 2-fluor-5-bromopyridine) were investigated. The boronic derivatives **4b** and **6** coupled to some of these heteroarylhalides in modest to low yield and compounds **11b–d**, and **10b**,**c** were synthesized (Schemes 5 and 3). The reaction of triazoloisoquinoline boronic acid **6** with iodoanisol and with 2-bromothiophen resulted in a competitive formation of homo-coupling derivative **9**. In all reactions studied the protodeboronation is always the main result. The analytical and spectroscopic data for all new compounds are in Tables 1–3.

Protodeboronation is a known issue for heteroarylboronic acids, specifically when the boron is on a carbon adjacent to a heteroatom.[17] Triazolopyridines are easily quaternizated in N2,[18,19] and as Stevens et al. suggest for pyridineboronic

Table 1. ^{1}H NMR shifts (ppm) and *J* values (Hz) for triazolopyridine derivatives

	H3	H4	H5	H6	Others
3a[a]	7.90, s	7.53, d, *J*=8, 7 Hz	7.17, dd, J_1=8.7 Hz, J_2=6.7 Hz	6.98, d, *J*=6.7 Hz	
3b[a]	—	7.59, d, *J*=8.7 Hz	7.28, dd, J_1=8.7 Hz, J_2=6.6 Hz	7.15, d, *J*=6.6 Hz	2.54, s, (CH_3)
3c[b]	—	8.75, d, *J*=8.9 Hz	7.52, dd, J_1=8.9 Hz, J_2=6.8 Hz	7.66, d, *J*=6.8 Hz	8.59, d, *J*=4.8 Hz, H6′; 8.22, d, *J*=8.1 Hz, H3′; 7.82, dd, J_1=7.7 Hz, J_2=8.1 Hz, H4′; 7.23, dd, J_1=4.8 Hz, J_2=7.7 Hz, H5′
4a[c]	8.04, s	7.73, d, *J*=8.9 Hz	7.13, dd, J_1=8.9 Hz, J_2=6.6 Hz	7.43, d, *J*=6.6 Hz	1.38, s, 4(CH_3)
4b[c]	—	7.60, d, *J*=8.9 Hz	7.05, dd, J_1=8.9 Hz, J_2=6.6 Hz	7.40, d, *J*=6.6 Hz	1.37, s, 4(CH_3)
4c[c]	—	8.76, d, *J*=8.9 Hz	7.26, dd, J_1=8.9 Hz, J_2=6.6 Hz	7.46, d, *J*=6.6 Hz	8.59, d, *J*=4.9 Hz, H6′; 8.32, d, *J*=7.9 Hz, H3′; 7.72, t, *J*=7.7 Hz, H4′; 7.14, dd, J_1=4.9 Hz, J_2=7.5 Hz, H5′
5[c,d]	—	7.51, d, *J*=8.7 Hz	7.12, dd, J_1=8.7 Hz, J_2=6.3 Hz	7.36, d, *J*=6.3 Hz	4.27, m, 4H; 3.61, m, 2H; 3.32, m, 2H; 2.70, s, 3H; 2.59, s, 3H
11a[c]	—	7.50, d, *J*=8.8 Hz	7.17, dd, J_1=8.8 Hz, J_2=6.9 Hz	6.89, d, *J*=6.9 Hz	7.92, d, *J*=9.0 Hz, H2′+H6′; 7.00, d, *J*=9.0 Hz, H3′+H5′; 3.83, s, (OCH_3); 2.59, s, (CH_3)
11b[c,d]	—	7.71, d, *J*=8.8 Hz	7.31, dd, J_1=8.8 Hz, J_2=6.8 Hz	7.14, d, *J*=6.8 Hz	8.82, d, *J*=5.6 Hz, H2′+H6′; 7.99, d, *J*=5.6 Hz, H3′+H5′; 2.68, s, (CH_3)
11c[c,d]	—	7.69, d, *J*=8.8 Hz	7.30, dd, J_1=8.8 Hz, J_2=6.8 Hz	7.07, d, *J*=6.8 Hz	8.88, d, *J*=2.3 Hz, H6′; 8.55, dd, J_1=8.4 Hz, J_2=2.3 Hz, H4′; 7.53, d, *J*=8.4 Hz, H3′; 2.68, s, (CH_3)
11d[c,d]	—	7.68, d, *J*=8.9 Hz	7.30, dd, J_1=8.9 Hz, J_2=6.8 Hz	7.05, d, *J*=6.8 Hz	8.72, d, *J*=2.5 Hz, H6′; 8.67, ddd, J_{HF}=9.0 Hz, J_1=8.6 Hz, J_2=2.5 Hz; 7.14, dd, J_{HF}=2.8 Hz, *J*=8.6 Hz; 2.68, s, (CH_3)

[a] Solvent: D$_2$O/NaOH.
[b] Solvent: CD_3COCD_3.
[c] Solvent: Cl_3CD.
[d] NMR spectrum 400 MHz.

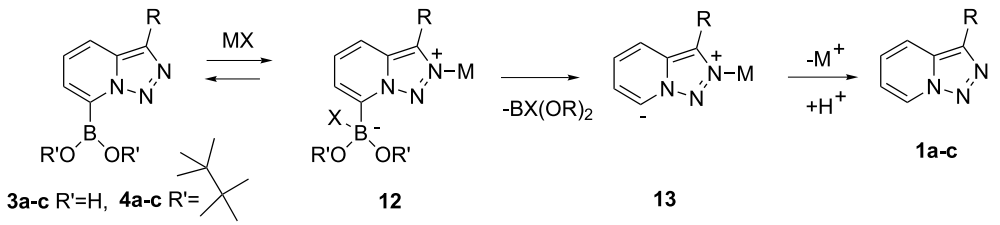
Table 2. ^{1}H NMR shifts (ppm) and J values (Hz) for triazoloisoquinoline derivatives

	H1	H6	H7	H8	H9	H10	Others
6[a]	8.36, s	7.20, s	7.66, d, J=7.3 Hz	⟨7.48–7.36, m⟩		7.96, d, J=7.6 Hz	
10a[b]	8.45, s	7.15, s	7.76, dd, J_1=7.4 Hz, J_2=2.9 Hz	⟨7.62–7.49, m⟩		8.12, dd, J_1=7.4 Hz, J_2=2.9 Hz	7.87, d, J=8.7 Hz, 2H; 7.20, d, J=8.7 Hz, 2H; 3.8, s, 3H
10b[b]	8.47, s	7.47, s	7.78–7.75 m	⟨7.58–7.55, m⟩		8.11–8.08, m	8.23, dd, J_1=3.7 Hz, J_2=1.5 Hz; 7.48, dd, J_1=5.1 Hz, J_2=1.5 Hz; 7.18, dd, J_1=5.1 Hz, J_2=3.7 Hz
10c[b]	8.47, s	7.28, s	7.81, dd, J_1=7.5 Hz, J_2=2.2 Hz	⟨7.68–7.59, m⟩		8.14, dd, J_1=7.5 Hz, J_2=2.2 Hz	9.08, s_{br}; 8.71, dd, J_1=4.5 Hz, J_2=1.5 Hz; 8.48, ddd, J_1=7.5 Hz, J_2=1.5 Hz, J_3=1.5 Hz; 7.47, dd, J_1=7.5 Hz, J_2=4.5 Hz

[a] Solvent: D_2O/NaOH.
[b] Solvent: Cl_3CD.

Table 3. Mass spectroscopic data, melting points, and preparative yields for new compounds

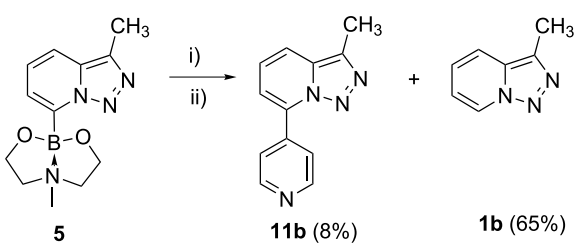
	Formula	MS	Mp (°C)	Yield %
3a	$C_6H_6BN_3O_2$	ESI 163, MW 163	>300	66
3b	$C_7H_8BN_3O_2$	ESI 177, MW 177	>300	40
3c	$C_{11}H_9BN_4O_2$	ESI 240, MW 240	>300	78
4a	$C_{12}H_{16}BN_3O_2$	HRMS found 245.1340, calcd 245.1335	72–74	65
4b	$C_{13}H_{18}BN_3O_2$	HRMS found 259.1243, calcd 259.1492	77–79	55
4c	$C_{17}H_{19}BN_4O_2$	HRMS found 322.1602, calcd 322.1601	185–187	31
5	$C_{12}H_{17}BN_4O_2$	HRMS found 260.0804, calcd 260.1441	130–132	90
11a	$C_{14}H_{13}N_3O$	HRMS found 239.1134, calcd 239.1059	134–136	20
11b	$C_{12}H_{10}N_4$	HRMS found 210.0941, calcd 210.0905	132–134	18
11c	$C_{12}H_9ClN_4$	HRMS found 244.0337, calcd 244.0516	178–180	10
11d	$C_{12}H_9FN_4$	HRMS found 228.0596, calcd 228.0811	206–208	15
10a	$C_{17}H_{13}N_3O$	HRMS found 275.1059, calcd 275.1056	117–120	25
10b	$C_{14}H_9N_3S$	HRMS found 251.0517, calcd 251.0518	131–132	26
10c	$C_{15}H_{10}N_4$	HRMS found 246.0905, calcd 246.0912	208–209	5



Scheme 6.

ester,[20] it is possible that the boronic derivatives **3** and **4** coordinate to Lewis acids and bases present in solution forming the zwitterions **12** that through ylides **13** gave triazolopyridines (Scheme 6).

In another hand, the ester **5** possess a tetra-coordinated boron which can no interact with other atom, for this we thought it could be better substrate for coupling reactions.[21]



Scheme 7. i, 4-iodopyridine/$Pd(PPh_3)_4$/dioxane; ii, $Ba(OH)_2.8H_2O$/H_2O/H_2O/90–100 °C, 20 h.

We tried the reaction of **5** with 4-iodopyridine using the best conditions found in the reaction of **4b** with the same co-reagent, nevertheless compound **11b** was obtained in smaller yield (8%) and triazolopyridine **1b** was also formed (65% yield) (Scheme 7).

3. Conclusion

In summary, we have successfully formed and characterized some 7-triazolopyridylboronic acids and esters, that are stable solids when have been stored, as well as 5-triazolo-isoquinolylboronic acid. Nevertheless, in solution under the various Suzuki reaction conditions experimented they are not very stable and underwent protodeboronation. 7-Triazolopyridylboronic acids are the most unstable compounds. Still we were able to synthesize some new 7-aryltriazolopyrines and 5-aryltriazolisoquinolines in modest to low yields, as result of Suzuki type cross-coupling reactions. Investigations are continuing on boronic

esters to improve these yields by study of the recently developed methodologies, a solventless Suzuki coupling reaction,[21] and an in situ formation and reaction of heteroarylboronic esters.[20,22]

4. Experimental

Melting points were determined on a Kofler heated stage and are uncorrected. NMR spectra were recorded on a Bruker AC300 MHz or on a JEOL Lambda 400 MHz spectrometers. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons). ESI-MS was performed using an ion trap mass spectrometer (Esquire 3000 Plus, Bruker) coupled to a liquid chromatograph (Agilet LC 1100 Chemstation), the ionization method was electrospray with positive ion polarity (ESI+). Samples were dissolved in acetonitrile/water (2/3) containing 0.5% formic acid. Infrared spectra were recorded in KBr discs on a Bio-Rad FTS-7. Chromatography was performed on a Chromatotron, using 2 cm plates of silica Merck Pf254. $Pd(PPh_3)_4$ supplier Lancaster.

4.1. General procedure for preparation of boronic acids

To a 2.5 M solution of *n*-BuLi (1.2 equiv.) in hexane, cooled to −40 °C, was added a solution of the corresponding triazoloazine (1 equiv.) in dry toluene and the solution kept at this temperature 4 h. A solution of triisopropyl borate (1.2 equiv.) in toluene was then added and the mixture was allowed to react at this temperature for over 2 h, and then allowed to warm to room temperature. The mixture was quenched by slow addition of 5% aqueous NaOH solution. The resulting aqueous layer was collected and acidified to pH=5 by dropwise addition of concentrated HCl, keeping the internal temperature below 5 °C. Extraction with ethyl acetate, evaporation of the organic layer and washing with ether gave the corresponding boronic acids.

4.1.1. 7-[1,2,3]Triazolo[1,5-*a*]pyridylboronic acid 3a. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3201, 1352, 822, 756. ^{13}C NMR δ (D_2O/NaOH) 130.00 (C), 126.79 (CH), 124.96 (CH), 119.00 (C), 118.23 (CH), 115.32 (CH). MS *m*/*z* 163, 145, 135.

4.1.2. 7-(3-Methyl-[1,2,3]triazolo[1,5-*a*]pyridyl)boronic acid 3b. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3423, 1316, 868, 772. ^{13}C NMR δ (D_2O/NaOH) 133.80 (CH), 132.08 (C), 125.52 (CH), 118.09 (CH), 117.00 (C), 114.81 (CH), 9.49 (CH_3). MS *m*/*z* 177, 159, 149, 131.

4.1.3. 7-[3-(2-Pyridyl)-[1,2,3]triazolo[1,5-*a*]pyridyl]-boronic acid 3c. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3368, 1316, 830, 753. MS *m*/*z* 240, 212, 194.

4.1.4. [1,2,3]Triazolo[5,1-*a*]isoquinolylboronic acid 6. Prepared as described.[3]

4.2. General procedure for preparation of boronic pinacol esters

To a 2.5 M solution of *n*-BuLi (1.2 equiv.) in hexane, cooled to −40 °C, was added a solution of the corresponding triazoloazine (1 equiv.) in dry toluene and the solution kept at this temperature 4 h. A solution of triisopropyl borate (1.2 equiv.) in toluene was then added and the mixture was allowed to react at this temperature for over 2 h, and then allowed to warm to 0−5 °C. A solution of anhydrous pinacol (1.3 equiv.) in toluene was added and, after 5 min, a solution of glacial acetic acid (1.05 equiv.). The mixture was filtered through Celite, and extracted with 5% aqueous NaOH solution. The resulting aqueous layer was collected and acidified to pH=5 by dropwise addition of concentrated HCl, keeping the internal temperature below 5 °C. Extraction with dichloromethane, evaporation of the organic layer and washing with ether/hexane gave the corresponding dioxaborolanes.

4.2.1. 2-(7-[1,2,3]Triazolo[1,5-*a*]pyridyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane 4a. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3477, 1366, 1150, 979, 758. ^{13}C NMR δ ($CDCl_3$) 134.00 (C), 126.17 (CH), 125.84 (CH), 124.37 (CH), 120.92 (CH), 110.00 (C), 85.70 (C)×2, 24.20 (CH_3)×4. MS *m*/*z* 245, 217, 216, 118.

4.2.2. 2-(3-Methyl-7-[1,2,3]triazolo[1,5-*a*]pyridyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane 4b. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3410, 1329, 1134, 978, 738. ^{13}C NMR δ ($CDCl_3$) 133.57 (C), 131.02 (C), 125.08 (CH), 124.84 (CH), 123.04 (CH), 120.52 (CH), 84.51 (C×2), 24.64 (CH_3×4), 9.96 (CH_3). MS *m*/*z* 259, 231, 216, 188, 172, 149, 132.

4.2.3. 2-[3-(2-Pyridyl)-7-[1,2,3]Triazolo[1,5-*a*]pyridyl]-4,4,5,5-tetramethyl[1,3,2]dioxaborolane 4c. Yellow solid. IR ν_{max} (KBr) (cm^{-1}) 3468, 1378, 1179, 846, 739. ^{13}C NMR δ ($CDCl_3$) 153.00 (C), 149.44 (C), 137.09 (CH), 132.23 (C), 127.00 (C), 126.18 (CH), 125.65 (CH), 124.13 (CH), 122.27 (CH), 121.12 (CH), 96.94 (C), 85.69 (C×2), 23.45 (CH_3×4). MS *m*/*z* 322, 295, 195, 168.

4.3. 2-(3-Methyl-7-[1,2,3]triazolo[1,5-*a*]pyridyl)-1,3,6-dioxazaborolane 5

To a mixture of 3-methyl-7-triazolopyridylboronic acid **3a** (516 mg, 2.91 mmol) and $MgSO_4$ (ca. 1 g per mmol) in dry dichloromethane (50 mL) was added dropwise a solution of N-methyldiethanolamine (365 mg, 3.08 mmol) in dichloromethane. The mixture was allowed to react under stirring at room temperature for 48 h. Then the mixture was filtered under reduced pressure. The filtrate was dried over $MgSO_4$ and concentrated to dryness. A yellow oil was obtained that was precipitate by ethyl acetate/ether, after filtration compound **5** was obtained almost pure as a yellow solid (655 mg, 87%). ^{13}C NMR δ ($CDCl_3$) 133.11 (C), 131.90 (C), 123.58 (CH), 121.28 (CH), 116.46 (CH), 62.58 (CH_2×2), 61.16 (CH_2×2), 44.46 (CH_3), 10.36 (CH_3). MS *m*/*z* 260, 259, 232, 231, 217, 216, 132, 128, 127, 104.

4.4. General procedure for preparation of 5-aryl-[1,2,3]triazolo[5,1-*a*]isoquinolines

A mixture of 5-[1,2,3]triazolo[5,1-*a*]isoquinolylboronic acid **6** (85 mg, 0.4 mmol), DME (10 mL), sodium hydrogen carbonate (100 mg, 1.2 mmol) and water (5 mL), was heated at 45 °C under nitrogen atmosphere with vigorous

stirring (15 min). A solution of the corresponding co-reactive (0.3 mmol), and $Pd[PPh_3]_4$ (23 mg, 0.039 mmol) in DME (5 mL) was added. The reaction mixture was heated to reflux with vigorous stirring under nitrogen atmosphere, the rate of reaction was followed by TLC. (6 h). Water was added (50 mL) and the mixture was extracted with dichloromethane (3×50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The reaction crude was purified by chromatotron using ethyl acetate/hexane in increasing amounts as eluent.

4.4.1. 5-(4-Methoxyphenyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline 10a. The co-reactive was 4-iodoanisol (58 mg). The isolated products were: [1,2,3]triazolo[5,1-*a*]isoquinoline **2** (21 mg, 31%), 5-(4-methoxyphenyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline **10a** (27 mg, 25%). ^{13}C NMR δ ($CDCl_3$) 160.62 (C), 135.75 (C), 133.20 (C), 130.64 (CH), 129.65 (CH), 128.92 (CH), 128.02 (CH), 127.16 (CH), 125.89 (C), 124.31 (CH), 123.66 (CH), 121.93 (C), 114.59 (CH), 113.83 (CH), 55.24 (OCH_3). MS *m*/*z* 275, 247, 232, 203, and 5,5′-bi[1,2,3]triazolo[5,1-*a*] isoquinoline **9** (20 mg, 30%).

4.4.2. 5-(2-Thienyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline 10b. The co-reactive was 2-bromothiophene (57 mg). The isolated products were: [1,2,3]triazolo[5,1-*a*]isoquinoline **2** (18 mg, 26%), 5-(2-thienyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline **10b** (26 mg, 26%). ^{13}C NMR δ ($CDCl_3$) 132.15 (C), 132.14 (C), 128.89 (CH), 128.57 (CH), 128.33 (CH), 127.54 (CH), 127.29 (CH), 126.82 (CH), 126.53 (CH), 125.21 (CH), 122.91 (C), 121.96 (C), 112.58 (CH). MS *m*/*z* 251, 223, 222, 190, and 5,5′-bi[1,2,3]triazolo[5,1-*a*]isoquinoline **9** (25 mg, 36%).

4.4.3. 5-(3-Pyridyl)-[1,2,3]triazolo[5,1-*a*]isoquinoline 10c. The co-reactive was 3-bromopyridine (78 mg). The isolated products were: triphenylphosphine oxide (18 mg), [1,2,3]triazolo[5,1-*a*]isoquinoline **2** (23 mg, 35%), 5-(3-pyridyl)-[1,2,3]triazolo[5,1-*a*] isoquinoline **10c** (5 mg, 5%). ^{13}C NMR δ (Cl_3CD) (DEPT) 148.44 (CH), 148.21 (CH), 138.14 (CH), 130.20 (CH), 129.71 (CH), 129.62 (CH), 128.79 (CH), 128.28 (CH), 124.43 (CH), 116.84 (CH). MS *m*/*z* 246, 218.

4.5. General procedure for preparation of 7-aryl-3-methyl-[1,2,3]triazolo[1,5-*a*] pyridines

A mixture of 2-(3-methyl-7-[1,2,3]triazolo[1,5-*a*]pyridyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane **4b** (mg, mmol), the corresponding co-reactive (mmol), and $Pd[PPh_3]_4$ as catalyst (mg, %) was dissolved in the appropriate solvent (mL), then a base (g, mmol) dissolved in water (mL) was added and the mixture was heated (°C) with vigorous stirring (h), the rate of reaction was followed by TLC, and then was cooled to room temperature. Water was added (mL) and the mixture was extracted with a organic solvent. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The reaction crude was purified by chromatotron or column chromatography using ethyl acetate/hexane in increasing amounts as eluent.

4.5.1. 7-(4-Methoxyphenyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11a. Starting material **4b** (100 mg, 0.4 mmol), 4-iodoanisol as co-reactive (0.32 mmol), catalyst (33 mg, 5%), DMF as solvent (7 mL), K_3PO_4 as base (103 mg, 0.48 mmol), water (7 mL), temperature (70 °C), time (16 h), water (5 mL), extraction solvent ethyl acetate. Purified by chromatotron, the isolated products were: triphenylphosphine oxide (17 mg), 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b** (37 mg, 70%), 7-(4-methoxyphenyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11a** (19 mg, 20%). IR ν_{max} (KBr) (cm^{-1}) 1636, 1606, 1505, 1283. ^{13}C NMR δ ($CDCl_3$) 161.25 (C), 138.46 (C), 134.85 (C), 133.07 (C), 130.97 (CH×2), 129.00 (C), 124.95 (CH), 124.48 (CH), 115.84 (CH), 114.51 (CH×2), 55.52 (CH_3), 10.92 (CH_3). MS *m*/*z* 239, 227, 211, 196, 185, 168.

4.5.2. 7-(4-Pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11b. Starting material **4b** (205 mg, 0.8 mmol), 4-iodopyridine as co-reactive (0.7 mmol), catalyst (40 mg, 5%), dioxane as solvent (25 mL), $Ba(OH)_2.8H_2O$ as base (224 mg, 0.71 mmol), water (4 mL), temperature (90–100 °C), time (20 h), water (5 mL), extraction solvent dichloromethane. Purified by column chromatography, the isolated products were: 3-methyl-[1,2,3]triazolo[1,5-*a*]-pyridine **1b** (58 mg, 55%), 7-(4-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11b** (30 mg, 18%). IR ν_{max} (KBr) (cm^{-1}) 1606,1572, 1553, 1424, 1401, 783. ^{13}C NMR δ ($CDCl_3$) 150.38 (CH×2), 139.49 (C), 135.40 (C), 135.19 (C), 132.61 (C), 123.81 (CH), 123.00 (CH×2), 117.97 (CH), 115.87 (CH), 10.48 (CH_3). MS *m*/*z* 210, 182, 181, 155, 78.

4.5.3. 7-(2-Chloro-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11c. Starting material **4b** (315 mg, 1.21 mmol), 2-chloro-5-iodopyridine as co-reactive (310 mg, 1.3 mmol), catalyst (60 mg, 4%), dioxane as solvent (40 mL), $Ba(OH)_2{\cdot}8H_2O$ as base (400 mg), water (8 mL), temperature (80–100 °C), time (24 h), water (5 mL), extraction solvent dichloromethane. Purified by column chromatography, the isolated products were: 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b** (100 mg, 62%), 7-(2-chloro-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11c** (30 mg, 10%). IR ν_{max} (KBr) (cm^{-1}) 1633,1588, 1556, 1112, 783. ^{13}C NMR δ ($CDCl_3$) 152.62 (C), 149.29 (CH), 139.27 (CH), 135.26 (C), 133.76 (C), 132.53 (C), 127.24 (C), 124.03 (CH), 123.89 (CH), 117.55 (CH), 115.33 (CH), 10.46 (CH_3). MS *m*/*z* 246, 244, 218, 217, 216, 215, 191, 189, 181, 78.

4.5.4. 7-(2-Fluor-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine 11d. Starting material **4b** (400 mg, 1.54 mmol), 5-bromo-2-fluorpyridine as co-reactive (246 mg, 1.4 mmol), catalyst (80 mg, 5%), dioxane as solvent (20 mL), $Ba(OH)_2{\cdot}8H_2O$ as base (2.8 mmol), water (4 mL), temperature (50–60 °C), time (72 h), water (5 mL), extraction solvent dichloromethane. Purified by column chromatography using cyclohexane/ethyl acetate/methanol in increasing amounts as eluent, the isolated products were: 3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **1b** (143 mg, 70%), 7-(2-fluor-5-pyridyl)-3-methyl-[1,2,3]triazolo[1,5-*a*]pyridine **11d** (53 mg, 15%). IR ν_{max} (KBr) (cm^{-1}) 1635,1598, 1486, 1257, 793. ^{13}C NMR δ ($CDCl_3$) 164.00 (C) (d, $^1J_{CF}$=241.90 Hz), 147.89 (CH) (d, $^3J_{CF}$=14.96 Hz), 142.13 (CH) (d, $^3J_{CF}$=8.33 Hz), 135.25 (C), 133.88 (C), 132.56 (C), 126.48 (C) (d, $^4J_{CF}$=4.92 Hz),

123.96 (CH), 117.36 (CH), 115.19 (CH), 109.50 (CH) (d, $^2J_{CF}$=37.95 Hz), 10.49 (CH_3). MS *m*/*z* 228, 200, 199, 173.

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Second-generation synthesis of protected phosphonothiodifluoromethylene analogues of nucleoside-3′-phosphates

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Abstract—A practical, eight-step synthesis of the key intermediate **14** in 19% overall yield from α-D-xylose is described. The preparation can be carried out on multi-gram scale and involves the use of the organomagnesium reagent **2d**. The capability of derivative **14** to be transformed into the title compounds is examplified by the preparation of **15**. Additionally, X-ray crystallography of intermediate **12** provided the first structural data on difluorophosphonothioates.

Two decades ago Blackburn's and McKenna's pioneering work on α,α-difluoromethylphosphonates aimed at the development of an hydrolytically and enzymatically stable mimic of the phosphate group.[1] The strength of the P–C bond as well as both the size and the electronic nature of the fluorine atoms all contributed to reaching that goal.[2] Numerous applications have since then been described and, for instance, analogues of nucleosides mono-, di- and triphosphates incorporating this functional group have been prepared and reported to possess various bioactivities.[3] However, the reactivity of reagents such as the lithium salt of dialkyl difluoromethylphosphonate **1b** has sometimes restricted the generalized access to such analogues (Fig. 1).[4] For instance, inertness of **1b** toward secondary and tertiary halides has long kept scientists from successfully preparing difluorophosphonates bearing two substituents on the carbon atom next to the CF_2 unit. A number of solutions

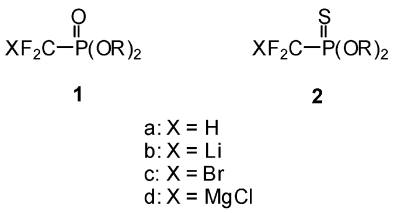

Figure 1. Structures of **1a**-**1d** and **2a**-**2d**.

to this problem have been published these past few years, relying on either addition of phosphorus-centered radicals onto *gem*-difluoroalkenes or reactions between organometallic species and electrophilic sp^2 carbon atoms.[5,6] Additional approaches have involved exploiting cycloaddition processes with activated dienophiles, dipolarophiles or dienes substituted with a phosphonodifluoromethyl unit, and coupling reactions with allylic substrates.[7,8] Another elegant methodology based on a coupling reaction with an halogenated sp^2 carbon/[3,3]-sigmatropic rearrangement sequence has been described by Percy and applied to the preparation of a 3,4-dideoxyribonolactone bearing a phosphonodifluoromethyl unit on carbon 3.[9] Our interest to use this functional group as a replacement of the phosphate in oligonucleotides (with implications in the antisense and antigene strategies) led us to work out a first and efficient approach to the preparation of the title compounds, relying on the use of the lithium salt of diethyl difluoromethylphosphonothioate **2b** and the subsequent transformation of the P=S bond into a P=O bond.[10] Besides the stability of the C–P bond and the documented isosteric and isoelectronic natures of difluorophosphonates and phosphates, the effect of replacing the 3′-oxygen atom of a nucleotide with a CF_2 unit may play a significant role on the conformation of the ribose, in an oligomer. While it is known that the replacement of the oxygen with a less electronegative CH_2 moiety induces a more pronounced shift toward the required, usual 3′-*endo* ring pucker, it has been shown that simple phosphonates are not optimal, due, among others, to an increased interbase distance. The two fluorine atoms might thus have an indirect, positive effect on the adopted conformation of the ribose and on the stability

Keywords: Phosphonothiodifluoromethylene; Nucleotide analogue; Organomagnesium reagent.
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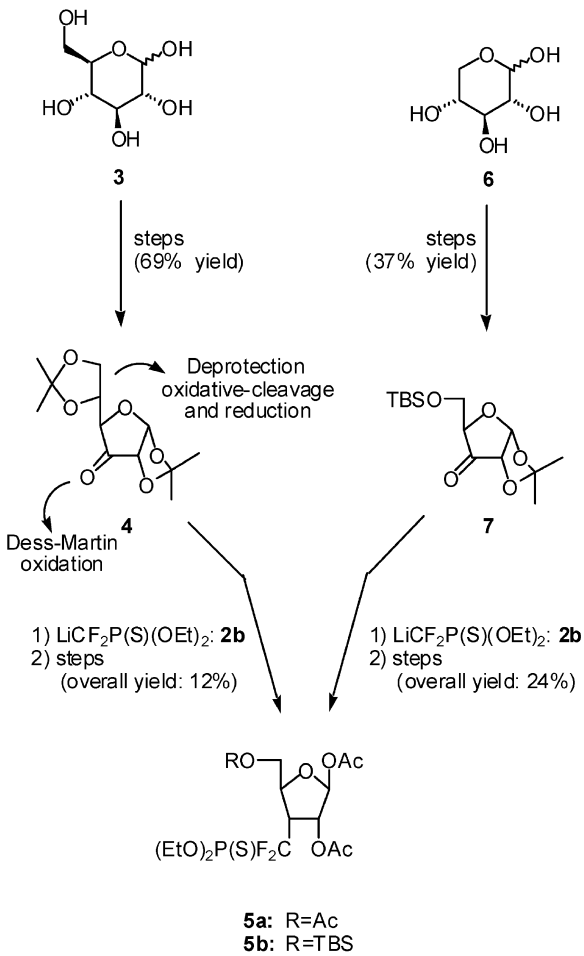
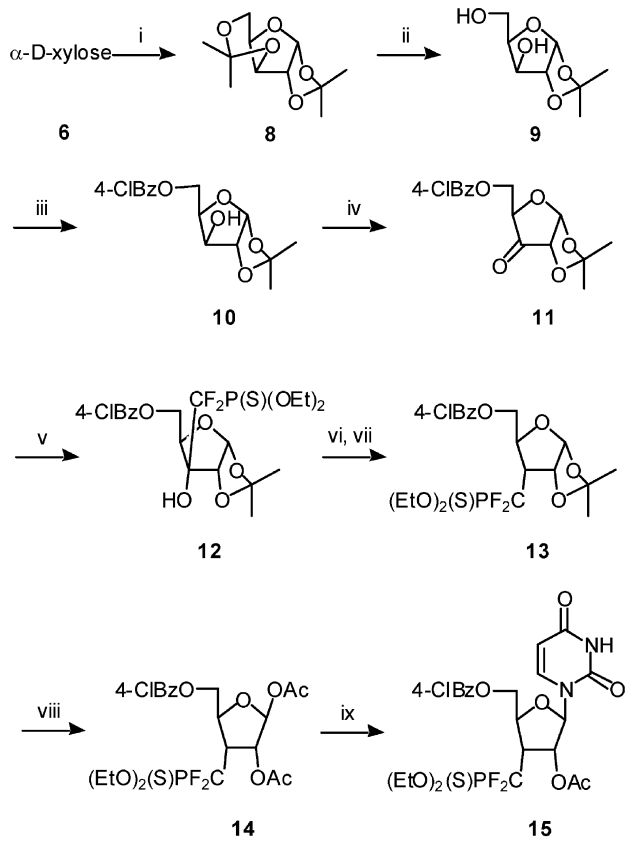


Scheme 1.



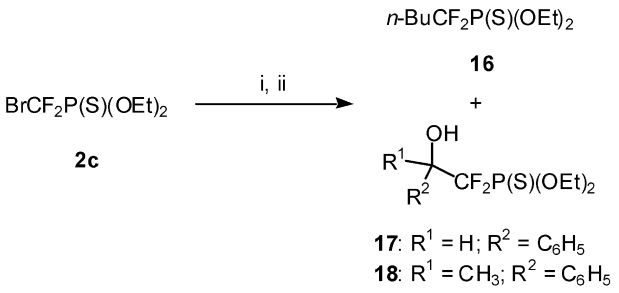
Scheme 2. Reagents and conditions: (i) acetone, $CuSO_4$, H_2SO_4; (ii) MeOH/HCl, or MeCN/H_2O, CAN (3 mol%); (iii) 4-ClBzCl, TEA, CH_2Cl_2; (iv) $C_3N_3O_3Cl_3$, TEMPO (4 mol%), CH_2Cl_2; (v) *iso*propMgCl, **2c**, THF, −45 °C; (vi) *iso*propMgCl, THF, 0 °C, then $ClCOCO_2Me$; (vii) $(n\text{-}Bu)_3SnH$/AIBN; toluene; (viii) AcOH/Ac_2O/H_2SO_4; (ix) (U)TMS/TMSOTf, 1,2-dichloroethane.

of the duplex RNA-oligomer.[11] The need for large amounts of the nucleotide analogues led us to develop a second-generation, more efficient preparation of the title compounds, the account of which is reported in this note.

Two substrates, namely α-D-glucose **3** and α-D-xylose **6**, had been selected in the first-generation synthesis (Scheme 1). These choices, while allowing us to get the target molecules, ultimately turned out to feature several drawbacks for a large scale preparation of a protected ribose encompassing a phosphonodifluoromethylene unit on carbon 3′. Thus, using the readily available α-D-glucose implied unavoidable functional group manipulation and oxidation of the 5,6-diol unit to get the 5-carbon ribose skeleton. In addition, the overall transformation included the use of the Dess–Martin reagent, and of *tert*-butyllithium, and required several separative purifications by chromatography. The six-step synthesis nevertheless delivered the key difluorophosphonothioate **5a** in 12% yield from **4** and translated into a global yield of 8% from α-D-glucose **3**. The synthetic route from α-D-xylose **6** suffered from the same use of *tert*-butyllithium and displayed similar efficiency, compound **5b** being isolated in 8% overall yield.[10]

This last preparation nevertheless constituted the basis for the second-generation synthesis. Classical protection of α-D-xylose **6** quantitatively furnished bisacetonide **8**, according to literature procedure (Scheme 2).[12] Selective, room temperature deprotection of the 3,5-*iso*propylidene unit was smoothly performed using cerium ammonium nitrate (CAN) and quantitatively afforded diol **9**.[13] The choice of a 4-chlorobenzoyl group to protect the primary alcohol stemmed from the known crystalline nature of both alcohol **10** and ketone **11**, and from the general propensity of such derivatives to be crystalline (vide infra).[14] Alcohol **10** was oxidized by a modification of Matsuda's procedure calling for the use of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO).[14,15]

The production of difluorophosphonothioate **12** was then tackled. The lithiated reagent **2b** is known to be efficiently generated from bromide **2c** via an halogen–metal exchange reaction involving *tert*-butyllithium.[10] The need to avoid the latter reagent led us to reinvestigate the alternative provided by the use of *n*-butyllithium (*n*-BuLi). Sequential addition of (i) *n*-BuLi and (ii) benzaldehyde to a solution of bromide **2c** in tetrahydrofuran (THF) at −78 °C invariably led to mixtures of **16** and **17**, the varying amount of **16** being directly proportional to the stirring time separating the additions of *n*-BuLi and benzaldehyde; not unexpectedly, the *n*-butyl bromide formed by the halogen–metal exchange process competitively reacted with **2b** (Scheme 3). Addition of *n*-BuLi to a mixture of **2c** and benzaldehyde reproducibly gave alcohol **17**, in fair isolated yield (60%) (Table 1, entry 1). Using acetophenone led to an essentially identical



Scheme 3. Reagents and conditions: (i) *n*-BuLi, −78 °C; (ii) benzaldehyde or acetophenone; H_3O^+.

Table 1. Yields of adducts from the reaction between **2b** or **2d** and benzaldehyde, acetophenone or ketone **11**

Entry	Reagent	Electrophile	Product	Yields (%)[a]
1	**2b**	C_6H_5CHO	**17**	60
2	**2b**	$C_6H_5C(O)Me$	**18**	57
3	**2b**	**11**	**12**	0
4	**2d**	C_6H_5CHO	**17**	75
5	**2d**	$C_6H_5C(O)Me$	**18**	54
6	**2d**	**11**	**12**	65–72

[a] Isolated yields.

result and alcohol **18** was isolated in 57% yield (entry 2). However, the use of the structurally and functionally more complex ketone **11** invariably led to intractable mixtures (entry 3). These unsatisfactory results prompted us to investigate the scope of the corresponding magnesium species **2d**. So far, this reagent has only been reported in the context of a relatively unsuccessful interaction with ketone **4**.[16] Attempts to directly generate **2d** from **2c** and activated magnesium at room temperature resulted in red–black solutions of unpredictable behavior and characterized by competing decomposition processes (^{19}F an ^{31}P NMR spectrometries). Halogen–metal exchange proved to be more effective: addition of a freshly prepared solution of *iso*propylmagnesium chloride in diethyl ether to a solution of **2c** in THF, followed by interaction of the resultant organomagnesium reagent **2d** with benzaldehyde led to the isolation of alcohol **17** in 75% yield (entry 4).[17] The use of acetophenone also led to the expected adduct **18**, albeit in a somewhat lower yield (entry 5).[18] To our delight, interaction between **2d** and ketone **11** delivered a single adduct in 65–72% isolated yield (entry 6).

The choice of the 4-chlorobenzoyl unit as protecting group turned out to be critical as (i) no product arising from a competitive reaction on the ester group was detected, and (ii) alcohol **12** crystallized upon standing, affording material suitable for X-ray analysis. The ORTEP drawing unambiguously demonstrates the total stereoselectivity of the process, resulting from the exclusive addition of **2d** on the convex face of **11** (Fig. 2). Some additional interesting features can be selected from the X-ray data. Thus, the $C^3–CF_2$ and $CF_2–P$ bond lengths (1.88 and 1.51 Å, respectively) compare favorably with values determined by Chambers and O'Hagan on α,α-difluorophosphonates (1.85 and 1.50 Å, respectively): the distances between these atoms are little influenced by the replacement of the double-bonded oxygen atom with a sulfur. The most interesting feature of difluorophosphonothioate seems to concern the

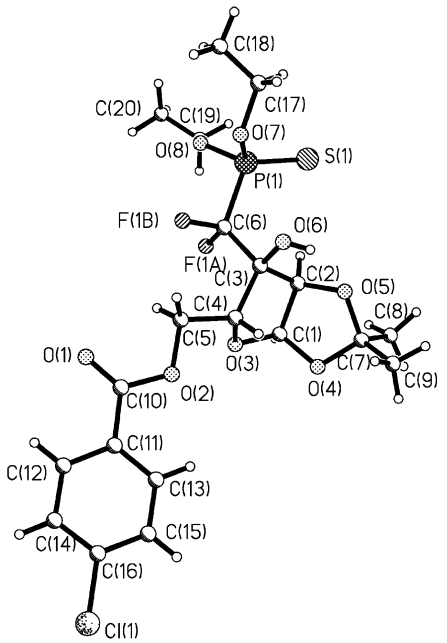


Figure 2. ORTEP drawing of adduct **12**.

angle formed by these two bonds: it is found to be 120.3° and is thus wider than those reported for both the phosphate (118.5°) and the difluorophosphonate (116.5°).

The deoxygenation radical process allowing the conversion of alcohol **12** into phosphonate **13** is based on our previous work.[10] This time however, *iso*propylmagnesium chloride was used as base instead of *n*-BuLi (Scheme 2). Quenching the alcoholate with methyl oxalyl chloride yielded the oxalate intermediate, which was treated with tri-*n*-butyltin hydride and a catalytic amount of azobis*iso*butyronitrile (AIBN), without further purification. Thus refluxing this mixture in toluene for 2 h led to the formation of **13** as the exclusive product. Again, hydrogen quenching of the intermediate radical occurred exclusively from the convex face to cleanly produce the stereochemical inversion at C-3. It is noteworthy that the tin by-products could be distilled off under vacuum from the crude mixture to leave the product virtually free from tin impurities.[19] Removal of the 1,2-isopropylidene group and protection of the hydroxyl functions as acetates was carried out in a single operation and delivered difluorophosphonothioate **14** in 77% isolated yield. Here again, silica was used to filter the product as no by-product was present in the crude material.

Finally, the capability of compound **14** to be transformed into a modified nucleoside was verified by using Vorbruggen's procedure.[20] Treatment of **14** with the bis-trimethylsilyl derivative of uracil under Lewis acid catalysis afforded the fully protected difluorophosphonothioate **15** (76% yield).

The key intermediate **14** was thus prepared from α-D-xylose in eight steps and 19% overall yield. The synthesis is easily amenable to multigram quantity scale as no separation by chromatography is required; the need for *tert*-BuLi has been eliminated by using the organomagnesium reagent **2d** and the use of the 4-chlorobenzoyl group allows easy Kugel–Rohr distillation of the tin by-products resulting from the

deoxygenation process. Additionally, it provided with a crystalline adduct **12** whose X-ray data yielded the first structural comparison between the difluorophosphonothioate and the corresponding fully oxygenated functional group.

1. Experimental

1.1. 1,2-*O*-*Iso*propylidene-α-D-xylofuranose (9)

To a solution of 1,2-3,5 di-*O*-*iso*propylidene-α-D-xylose (66 g, 0.287 mol) in HPLC grade water (265 mL) and acetonitrile (250 mL) is added CAN (4.7 g, 8.6 mmol, 3 mol%). The solution is stirred for 18 h at room temperature until monitoring by thin-layer chromatography (tlc) indicates completion. Aqueous ammonium hydroxide (NH_4OH) (20 mL) is added, the resultant yellow–orange suspension is filtered through a mixture of celite and silica (9/1 w/w) which is then washed with MeOH (150 mL). Evaporation of the volatiles under reduced pressure and lyophilisation of the resultant aqueous layer yield **9** as a pale yellow oil. (53.4 g, 98%), identical in every respect with a sample prepared according to literature procedures.[14]

1.2. 5-*O*-(4-Chlorobenzoyl)-1,2-*O*-*iso*propylidene-α-D-pentofuranose-3-urose (11)

Dichloromethane (950 mL), alcohol **10** (101 g, 0.31 mol) and trichlorocyanuric acid (110 g, 0.47 mol) are sequentially added under nitrogen into a 2 L round bottomed flask equipped with a mechanical stirrer and a condenser. TEMPO (2.0 g, 14 mmol, 4.5 mol%) is then added in 10 portions (caution: exothermic reaction) and the reaction is stirred for 12 h. The reaction mixture is filtered through celite and eluted with CH_2Cl_2 (2×250 mL). The organic layer is sequentially washed with saturated $NaHCO_3$ (100 mL), 1.0 M aqueous HCl (200 mL) and brine (200 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude brownish oil is dissolved in chloroform (100 mL), and added dropwise to vigorously stirred *n*-heptane (1 L). After completion of the addition, the flask is cooled down to 4 °C overnight and the pale yellow solid (67.0 g) is collected by filtration. Concentration of the mother liquor affords 27 g of brown oil that is purified as above from chloroform (27 mL) and *n*-heptane (270 mL) to give an additional 10.5 g batch (total yield: 77.5 g, 77%). Analytical data identical with those from the literature.[14]

1.2.1. 3-(*O*,*O*-Diethylphosphonothio)difluoromethyl-1,2-*O*-*iso*propylidene-5-*O*-(4-chlorobenzoyl)-α-D-*allo*furanose (12). *Iso*propylmagnesium chloride (47 mL of a 1.1 M solution in ether, 51.7 mmol) is added at room temperature to anhydrous THF (150 mL) under inert atmosphere and the solution is cooled down to −78 °C. A solution of **2c** (13 g, 46.0 mmol) in THF (100 mL) is slowly added. After 5 min, ketone **11** (10 g, 30.6 mmol) in THF (50 mL) is added dropwise over 10 min. After another 10 min period of time, the solution is warm up to −45 °C and stirred for 5 h. Saturated aqueous NH_4Cl (70 mL) is added and the resultant mixture is warmed up to room temperature. The solvent is then evaporated and the residue extracted with AcOEt (2×200 mL). The organic layer is dried over $MgSO_4$ and evaporated. Compound **2a** and unreacted substrate **2c** are removed by Kugel–Rohr distillation (90 °C/0.2 mbar) to leave 15.8 g of a residual brown oil. This product is then filtered through a 15 cm wide and 5 cm long silica path. Washing is carried out with a 1:7 mixture of ethyl acetate/cyclohexane (750 mL) to yield 10.6 g of **12** as a colorless oil that spontaneously crystallizes at room temperature (yield: 65%). Another run performed on a 5.0 g scale gave 72% yield of **12**. ^{1}H NMR (200 MHz) δ 7.96 (d, J=8.8 Hz, 2H); 7.37 (d, J=8.8 Hz, 2H); 5.92 (d, J=4.4 Hz, 1H); 5.29 (d, J=4.4 Hz, 1H); 4.70 (td, J=5.8, 12.4 Hz, 1H); 4.6 (td, J=3.0 Hz, 1H); 4.6–4.1 (m, 5H); 3.48 (s, 1H); 1.58(s, 3H); 1.4 (s, 3H); 1.34 (td, J=3.7 Hz, 6H). ^{13}C NMR (50 MHz) δ 165.0; 139.1; 131.0; 128.4; 128.1; 120.0 (ddd, J=174, 258, 276 Hz); 113.0; 104.4; 82.7; 80.9 (ddd, J=12.2, 21.2, 24.3 Hz); 78.6; 64.8 (d, J=6.0 Hz); 64.4 (d, J=6.0 Hz); 62.7 (d, J=12.1 Hz); 26.5; 26.2; 15.9; 15.8. ^{31}P NMR (81 MHz) δ 71.8 (t, J=99.0 Hz). ^{19}F NMR (188 MHz) δ 50.7 (dd, J=101, 113 Hz); 47.0 (dd, J=101, 113 Hz). IR (neat) 3519, 2989, 2939, 1726, 1592, 1378, 1273, 1090, 1013 cm^{-1}. $[\alpha]_D^{589}$=+21.6 (c=1.1, CH_2Cl_2). Mp=80–81 °C. Anal. Calcd for $C_{20}H_{26}ClF_2O_8PS$: C, 45.24; H, 4.90; S, 6.03. Found: C, 45.37; H, 4.96; S, 5.88.

1.2.2. 3-Deoxy-3-(*O*,*O*-diethylphosphonothio)difluoromethyl-1,2-*O*-*iso*propylidene-5-*O*-(4-chlorobenzoyl)-α-D-*ribo*furanose (13). *Iso*propylmagnesium chloride (9.7 mL of a 1.3 M solution in ether, 12.6 mmol) is added at 0 °C to THF (55 mL) under inert atmosphere. Alcohol **12** (5.7 g, 10.5 mmol) in THF (55 mL) is added dropwise and the resultant solution is stirred for 1 h at the same temperature before adding freshly distilled methyl oxalyl chloride (2.9 mL, 31.5 mmol). The solution is stirred for an additional 20 min at 0 °C, warmed up to room temperature and evaporated. The mixture is poured into water (35 mL) and extracted with AcOEt (100 mL). The separated organic layer is dried ($MgSO_4$) and evaporated under reduced pressure at 60 °C to give 6.56 g of a pale yellow oil. This crude material is dissolved in toluene (66 mL) and the solution is refluxed under nitrogen for 20 min. Tri-*n*-butyltin hydride (3.8 mL, 12.1 mmol) and AIBN (1.0 g, 5.4 mmol) are then added and the solution is refluxed for two more hours. The solution is evaporated and the residue is Kugel–Rohr distilled (130–140 °C, 0.2 mbar) to eliminate the tin by-products. The resultant, undistilled brownish oil is then filtered through silica (15 cm wide and 5 cm high) and washed with ethyl acetate/cyclohexane (1:20; 500 mL) to afford 3.4 g of **13** as a pale yellow liquid (64%). ^{1}H NMR (200 MHz) δ 7.95 (d, J=8.8 Hz, 2H); 7.37 (d, J=8.8 Hz, 2H); 5.81 (d, J=3, 4 Hz, 1H); 4.92 (t, J=3.4 Hz, 1H); 4.7 (m, 2H); 4.2 (m; 5H); 3.0 (m, 1H); 1.53 (s, 3H); 1.31 (s, 3H); 1.31 (t, J=7.0 Hz, 6H). ^{13}C NMR (50 MHz) δ 165.1; 139.4; 131.0; 128.6; 128.2; 119.6 (ddd, J=276, 258, 174 Hz); 113.0; 104.7; 79.5; 79.4 (d, J=7.6 Hz); 74.7 (dd, J=7.8, 3.3 Hz); 65.4; 65.2; 64.4 (dd, J=16.7, 4.5 Hz); 47,0 (td, J=21.2, 18.2 Hz); 26.7; 26.3; 16.1 (d, J=4.6 Hz); 15.9 (d, J=3.0 Hz). ^{31}P NMR (81 MHz) δ 73,8 (dd, J=102, 113 Hz). ^{19}F NMR (188 MHz) δ 60 (ddd, J=298, 112, 6.8 Hz); 49,0 (ddd, J=298, 102, 6.8 Hz). IR (Neat) 2986, 1724, 1595, 1381, 1274, 1117, 1020 cm^{-1}. $[\alpha]_D^{589}$=+42.4 (c=2.51; CH_2Cl_2). Anal. Calcd for $C_{20}H_{26}ClF_2O_7PS$: C, 46.64; H, 5.05; S, 6.22. Found: C, 46.13; H, 4.72; S, 5.94. HRMS (E.I., 70 eV). Calcd for $C_{19}H_{23}F_2O_7PSCl$: 499.0537. Found: 499.0558.

1.2.3. 5-*O*-(4-Chlorobenzoyl)-1,2-di-*O*-acetyl-3-deoxy-3-(*O*,*O*-diethylphosphonothio)difluoromethyl-β-D-*ribo*-furanose (14). Difluorophosphonothioate **13** (3.3 g, 6.4 mmol) is dissolved in a mixture of acetic acid (30 mL) and acetic anhydride (30 mL). The solution is cooled down to 0 °C and sulfuric acid (1 mL) is added. The solution is stirred at room temperature overnight. The stirring mixture is then added over 30 min to a cooled mixture of water (100 mL), $NaHCO_3$ (84 g), ice (100 g) and ethyl acetate (200 mL). After completion of the addition, the solution is warmed up to room temperature and stirred until the pH reaches 8–9. The organic layer is separated and the aqueous phase is extracted with ethyl acetate (250 mL). The combined organic layers are extracted with saturated $NaHCO_3$ (120 mL), washed with brine (25 mL) and dried over Na_2SO_4. Filtration through silica (6 cm wide and 3 cm long) and washing of the solid layer with ethyl acetate/cyclohexane (1:5) (300 mL) give 2.77 g (77%) of colorless, oily **14**. ^{1}H NMR (200 MHz) δ 8.0 (d, J=8.4 Hz, 1H); 7.4 (d, J=8.4 Hz, 1H); 6.05 (d, J=1.5 Hz, 1H); 4.48 (d, J=4.4 Hz, 1H); 4.9 (m, 1H); 4.75 (d, J=12.4 Hz, 1H); 4.4–4.1 (m, 5H); 3.6–3.4 (m, 1H); 2.09 (s, 3H); 1.90 (s, 3H); 1.32 (t, J=7.0 Hz, 3H); 1.31 (t, J=7.0 Hz, 3H). ^{13}C NMR (50 MHz) δ 169.4; 168.7; 164.9; 139.6; 131.0; 128.7; 128.1; 119.3 (ddd, J=276, 259, 179 Hz); 98.2; 77.5 (t, J=3.0 Hz); 75.0 (d, J=7.6 Hz); 65.2 (d, J=16.7 Hz); 65.2 (d, J=16.7 Hz); 64.6 (d, J=7.6 Hz); 43.1 (td, J=22.7, 19.7 Hz); 20.8; 20.7; 16.0; 15.9. ^{31}P NMR (81 MHz) δ 74.1 (dd, J=111.3, 102.3 Hz). ^{19}F NMR (188 MHz) δ 57.2 (ddd, J=298, 111.7, 10.2 Hz); 47.8 (ddd, J=298, 111.7, 20.3 Hz). IR (neat) 2959, 2927, 1753, 1728, 1595, 143, 1371, 1273, 1235, 1092, 1018 cm^{-1}. $[\alpha]_D^{589}$=+5.18 (c=2.8; CH_2Cl_2). Anal. Calcd for $C_{21}H_{26}ClF_2O_9PS$: C, 45.12; H, 4.66. Found: C, 45.01; H, 4.80.

1.2.4. 1-*N*-[2-*O*-Acetyl-5-(4-chlorobenzoyl)-3-deoxy-3-(*O*,*O*-diethylphosphonothio)difluoromethyl-β-D-ribo-furanosyl]uridine (15). TMSOTf (0.71 mL, 3.9 mmol) is added dropwise to a cold solution (0 °C) of **14** (441 mg, 0.79 mmol) and bis(trimethylsilyl)uracil (607 mg, 2.4 mmol) in dry 1,2-dichloroethane (15 mL). The mixture is stirred at room temperature during 3 h, after which period of time it is poured into CH_2Cl_2 (50 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer is dried over Na_2SO_4 and evaporated to give 420 mg of a thick oil. Chromatography on silica and elution with dichloromethane/methanol (98:2) give 367 mg (76%) of **15** as a white solid. ^{1}H NMR (200 MHz) δ 8.96 (s, 1H); 7.98 (d, J=8.8 Hz, 1H); 7.41 (d, J=8.8 Hz, 1H); 7.22 (d, J=3.3 Hz, 1H); 5.72 (d, J=4.7 Hz, 1H); 5.59 (dd, J=8.0, 2.2 Hz, 1H); 5.0 (s, 1H); 4.9–4.7 (m, 2H); 4.51 (dd, J=12.8, 4.4 Hz, 1H); 4.3–4.1 (m, 4H); 3.8 (m, 1H); 2.112 (s, 3H); 1.31 (t, J=7.3 Hz, 3H); 1.30 (t, J=7.3 Hz, 3H). ^{13}C NMR (50 MHz) δ 169.8; 165.1; 164.0; 149.7; 141.7; 139.6; 131.0; 128.8; 127.8; 119.5 (ddd, J=274, 262, 177 Hz); 102.5; 93.3; 77.1 (d, J=9 Hz); 75.3 (d, J=6 Hz); 65.0 (d, J=11 Hz); 64.7 (d, J=11 Hz); 64.3; 43.4 (q, J=18 Hz); 20.8; 16.0; 15.9. ^{31}P NMR (81 MHz) δ 73.8 (t, J=108 Hz). ^{19}F NMR (188 MHz) δ 56.1 (ddd, J=295, 108, 13.5 Hz); 49.9 (ddd, J=295, 108, 20.3 Hz). IR (neat) 2991, 1717, 1693, 1456, 1377, 1272, 1231, 1091, 1014 cm^{-1}. UV–vis λ_{max} (CH_2Cl_2) 245 nm. $[\alpha]_D^{589}$=+16.2° (c=1.4; CH_2Cl_2). Mp 62–64 °C. Anal. Calcd for $C_{20}H_{26}ClF_2O_7PS$: C, 45.22; H, 4.29; S, 5.25. Found: C, 45.19; H, 4.37; S, 5.14. HRMS (DCI, 200 eV) m/z. Calcd for $C_{23}H_{27}N_2O_9F_2PSCl$ 611.0787. Found: 611.0831.

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Synthesis of *Amaryllidaceae* alkaloids, siculine, oxocrinine, epicrinine, and buflavine

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Abstract—Three crinane type of alkaloids isolated from *Amaryllidaceae* family were synthesized by taking advantage of the PIFA-mediated intramolecular *p*-*p*′ diphenol coupling reaction of norbelladine derivatives. Furthermore, buflavine was also prepared by using the *p*-*p*′ diphenol coupling followed by dienone–phenol rearrangement as a key step.

1. Introduction

Amaryllidaceae family is an attractive source of alkaloids,[1] which are valuable as targets for total synthesis because of their unique structures, limited supply, and promising bioactivities such as cholinesterase inhibition which has being found in galanthamine.[2,3] The alkaloids are, in the metabolic pathways, synthesized at least by three different types of intramolecular phenol coupling, that is, the coupling between the positions of *p*-*o*′, *p*-*p*′, and *o*-*p*′ (phenol–*O*-methylcathecol) in *O*-methylnorbelladine (**1**). Galanth-amine, for example, is one of the *p*-*o*′ coupling products while lycoline is generated via the *o*-*p*′ coupling.[4] By mimicking the biosynthetic phenol coupling, we have recently attained the total syntheses of galanthamine and narwedine, in which *O*-methylcathecol ring of **1** was replaced with 2-*O*-methylpyrogarrole in order to avoid the mixture of two products resulting from the *p*-*o*′ and the *p*-*p*′ coupling.[5] The *p*-*p*′ phenol coupling of **1** would generate maritidine (**2**), which was synthesized by several groups taking advantage of effective carbon–carbon bond formation such as oxidative phenol coupling[6] and Heck reaction[7] as key steps. Demethylation, epimerization, and/or formal oxidation of methoxy groups of maritidine (**2**) would provide crinine (**3**)[8] and its derivatives, for example, siculine (**4**) from *Sternbergia sicula*,[9] oxocrinine (**5**) isolated from *Crinum americanum*,[10] and epicrinine (**6**) from *Nerine bowdenii*[11] (Fig. 1).

These could be promising candidates as excellent lead compounds for pharmaceutical research since crinane,[12] the common structure of the crinine alkaloids, exhibited antivirus, antitumor, and anticholinergic activities.[13] Furthermore, it is also an acceptable hypothesis that buflavine (**7**) isolated from *Boophane flava*[14] might be also generated by the *p*-*p*′ coupling followed by dienone–phenol rearrangement. In this paper, we would like to report

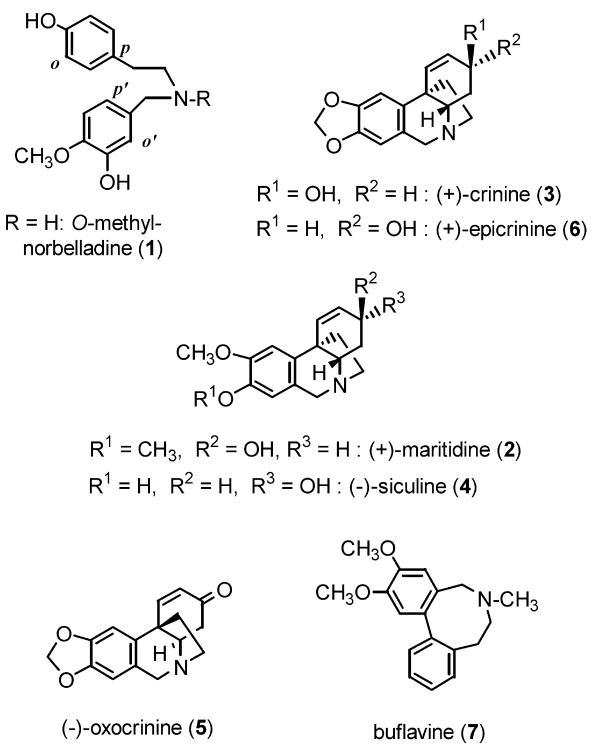

Figure 1. Structures of *Amaryllidaceae* alkaloids.

Keywords: Phenol coupling; Phenyliodine(III) bis(trifluoroacetate) (PIFA); Siculine; Oxocrinine; Epicrinine; Buflavine.
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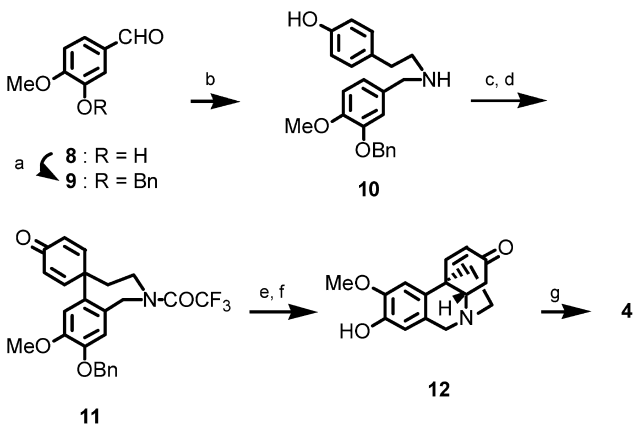


a: BnCl, K_2CO_3, DMF, 90 °C, 20 min., **b**: 1) tyramine, 2) $NaBH_4$, r.t., 1h. (82 % from **8**), **c**: $(CF_3CO)_2O$, pyridine, r.t., 1d. (quant.), **d**: PIFA, CF_3CH_2OH, -25 °C, 30 min. (78 %), **e**: BCl_3, CH_2Cl_2, -78 °C, 3d. (79 %), **f**: 10% KOH aq., r.t., 10 min. (87 %), **g**: L-Selectride, THF, - 78 °C, 1d. (53 %).

Scheme 1. Synthetic route of siculine (**4**).

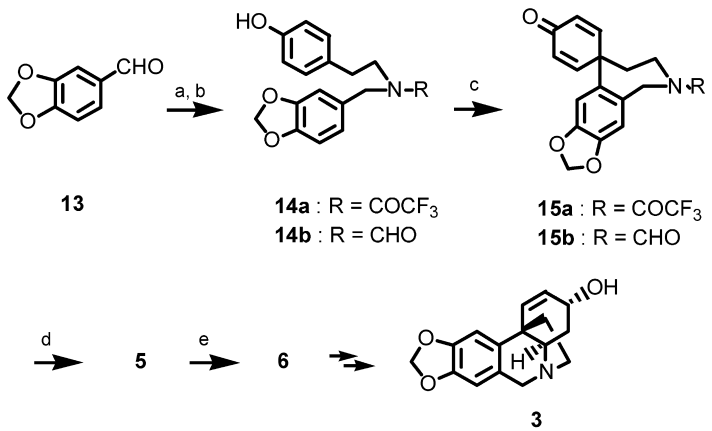
the facile synthesis of the alkaloids generated via the *p-p′* oxidative phenol coupling as a part of our synthetic studies of *Amaryllidaceae* alkaloids.

2. Result and discussion

We started our synthetic study of these alkaloids with the synthesis of siculine (**4**), of which synthetic studies have not been reported so far. After the protection of phenolic group of isovanillin (**8**) with benzyl group, obtained 3-*O*-benzylisovanillin (**9**) was exposed by reductive amination with tyramine in the presence of sodium borohydride to afford phenethylbenzylamine (**10**). Protection of the amino group of **10** with trifluoroacetyl group, followed by the oxidation with phenyliodine(III) bis(trifluoroacetate) (PIFA)[5,6c,d,15] proceeded the phenol coupling to afford dienone (**11**). Deprotection of the benzyl group of **11** with boron trichloride and successive hydrolysis of trifluoroacetylamide group with 10% potassium hydroxide in methanol gave the intramolecular Michael adduct (**12**). Reduction of **12** with L-Selectride afforded siculine (**4**) (Scheme 1).

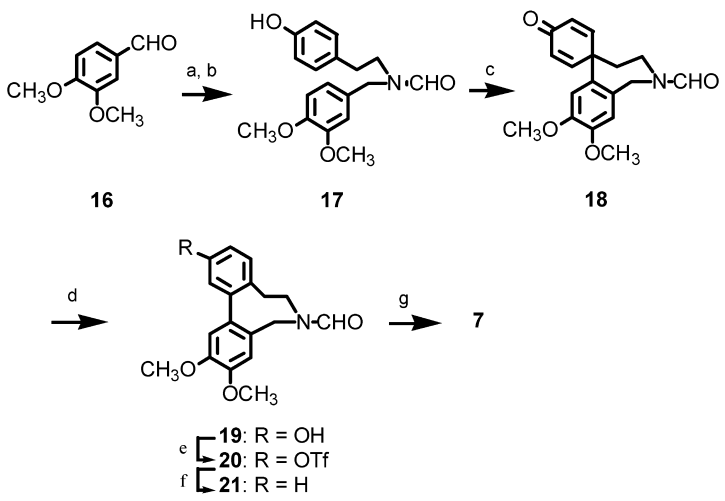
This strategy is also applicable to the synthesis of oxocrinine (**5**)[6i,16] and its related alkaloids. Reductive amination of piperonal (**13**) and tyramine was followed by *N*-acylation with either trifluoroacetic anhydride or ethyl formate to give **14a**, **14b**. The obtained **14a**, **14b** were, respectively, allowed to the oxidative coupling with PIFA giving the desired coupled products **15a**, **15b** in excellent yields. Respective hydrolysis of the protecting groups of **15a** and **15b** with 10% potassium hydroxide in methanol followed by spontaneous intramolecular Michael addition afforded oxocrinine (**5**), and successive reduction with L-Selectride gave epicrinine (**6**)[16a,17] that can be converted to crinine (**3**) by the known method (Scheme 2).[18]

Next, we tried to synthesize buflavine (**7**), which was prepared by Kobayashi 25 years prior to its isolation and characterization.[19] Since it has been isolated in 1995, buflavine (**7**) was synthesized by three groups using the biaryl coupling, that is, Meyers' coupling[20] and Suzuki–Miyaura coupling reactions.[21] However, tedious procedures were required to prepare arylborate or polymethoxybenzene derivatives before employing the coupling reactions. Being encouraged by the usefulness of the *p-p′* phenol coupling with PIFA for the synthesis of *Amallylidaceae* alkaloids as mentioned above, in addition to the previous reports,[5] we confirmed that applying the phenol coupling could effectively revise the synthetic route of **7**. Reductive amination of 3,4-dimethoxybenzaldehyde (**16**) with tyramine in the presence of sodium borohydride was first conducted to give the amine, and successive protection of the amino group with ethyl formate gave **17**. Unfortunately, oxidative coupling reactions that are reported to accompany



a: 1) tyramine, 2) $NaBH_4$, r.t., 1d., **b**: $(CF_3CO)_2O$ or HCO_2Et (quant. from **13**), **c**: PIFA, CF_3CH_2OH (**14a**: - 40 °C, 20 min., 74 %, **14b**: 0 °C, 30 min., 91 %), **d**: 10% KOH aq., MeOH (87 % from **15a**, 61 % from **15b**), **e:** L-Selectride, THF, - 78 °C, 1d. (82 %).

Scheme 2. Synthetic route of oxocrinine (**5**) and epicrinine (**6**).



a: 1) tyramine, r.t., 6h., 2) $NaBH_4$, r.t., 4h., **b**: HCO_2Et, reflux, 1d., (96 % from **16**), **c**: PIFA, r.t., 30 min., (92 %), **d**: methanesulfonic acid, r.t., 1d., (92 %), **e**: Tf_2O, 0 °C to r.t., 8h., (96 %), **f**: $Pd(OAc)_2$, PPh_3, Et_3N, HCO_2H, 60 °C, 2d., (87 %), **g**: $LiAlH_4$, r.t., 15h., (94 %).

Scheme 3. Synthetic route of buflavine (**7**).

eight-membered ring formation, for example, PIFA-mediated reaction with boron trifluoride etherate,[22] did not give any satisfactory results in this case. Therefore, the seven-membered product **18** of the *p*-*p*′ oxidative coupling of **17** with PIFA[18] was treated with methanesulfonic acid to convert it to **19** by dienone–phenol rearrangement.[6h] In order to deoxygenate the phenolic hydroxyl group, **19** was converted to triflate (**20**) followed by palladium-catalyzed reduction to afford **21**. Reduction of formamide group of **21** with lithium aluminum hydride gave buflavine (**7**) (Scheme 3). As expected, the overall yield of this synthetic route (64%) is much higher than those reported so far in the literatures.[20,21]

3. Conclusion

As mentioned above, we have succeeded in the first synthesis of siculine (**4**), the synthesis of buflavine (**7**) with the highest overall yield reported so far, and the short step synthesis of oxocrinine (**5**) and epicrinine (**6**), by applying the PIFA-mediated *p*-*p*′ diphenol coupling of norbelladine derivatives. The coupling reaction is applicable even on the industrial scale since it generates only volatile iodobenzene and trifluoroacetic acid. Further study on the synthesis of chiral compounds of **3**–**6** is now in progress.

4. Experimental

4.1. General

Melting points were taken on a micro hot-stage apparatus (Yanagimoto) and were uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8300 diffraction grating infrared spectrophotometer and ^1H- and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300, a Varian Unity INOVA-400 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a JEOL JMS-SX 102A QQ or a JEOL JMS-GC-mate mass spectrometer. Combustion analysis was done on a Perkin–Elmer Series II CHNS/O Analyzer 2400. Specific rotations were recorded on a Horiba SEPA-200 automatic digital polarimeter. Their data were recorded with Shimadzu C-R6A Chromatopac. Acetate buffer was adjusted with a Horiba pH meter F-13. Wakogel C-200 (silica gel) (100–200 mesh, Wako) was used for open column chromatography. Flash column chromatography was performed with Silica Gel 60N (Kanto Chemical Co., Inc.). Silica gel 60 F-254 plates (Merck) were used for thin layer chromatography (TLC). Preparative TLC (PTLC) was done with Silica gel 60 F-254 plate (0.25 mm, Merck) or Silica gel 60 F-254 plate (0.5 mm, Merck). When necessary, compounds were further purified by a recycle HPLC (JAI LC-908) on GPC column (JAIGEL 1H and 2H) after purification on silica gel.

4.2. Materials

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH_2, after washing with water 10 times, to remove methanol contaminants. Most of the reagents were obtained from Wako Pure Chemical Industries, Ltd., Nakalai Tesque, Inc., Aldrich Chemical Inc.

4.2.1. *N*-3′-Benzyloxy-4′-methoxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (10). Potassium carbonate (4.4 g, 32.0 mmol) and benzyl chloride (2.3 mL, 19.6 mmol) were successively added to a solution of isovanillin (**8**) (2.5 g, 16.3 mmol) in *N*,*N*-dimethylformamide (16 mL), and the reaction mixture was stirred for 3 h at 90 °C. After the reaction, the mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and

concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 3/1) afforded 3′-*O*-benzylisovanillin (**9**). Tyramine (2.9 g, 21.0 mmol) was added to a solution of **9** in methanol (40 mL), and the reaction mixture was stood to stir for 1 day. Sodium borohydride (728.2 mg, 19.2 mmol) was added to the reaction mixture at 0 °C and the mixture was stirred for another 3 h at room temperature. Crystal needles (**10**) (4.8 g, 82%) appearing in the reaction vessel were collected by filtration. Mp 135–136 °C (methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.23 (m, 5H), 6.96 (d, J=8.6 Hz, 2H), 6.86 (s, 1H), 6.78 (s, 2H), 6.65 (d, J=8.6 Hz, 2H), 4.98 (s, 2H), 3.83 (s, 3H), 3.68 (s, 2H), 2.81 (t, J=6.8 Hz, 2H), 2.71 (t, J=6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.23, 148.80, 148.12, 137.02, 131.50, 130.22, 129.71, 128.42, 127.73 127.38 121.13, 115.71, 114.17, 111.62, 70.69, 56.00, 53.25, 49.92, 34.60; IR ($CHCl_3$): 1612, 1593, 1514 cm^{-1}; HRMS calcd for $C_{23}H_{25}NO_3$ (M^+): 363.1834, found: 363.1838. Anal. Calcd for $C_{23}H_{25}NO_3$: C, 76.01; H, 6.93; N, 3.85. Found: C, 76.02; H, 6.94; N, 3.82.

4.2.2. Preparation of dienone (11). Trifluoroacetic anhydride (0.93 mL, 6.6 mmol) was added to a solution of **10** (1.0 g, 2.8 mmol) in pyridine (10 mL) at 0 °C. The reaction mixture was stirred for 1 day at 0 °C, and then the methanol was added to quench the reaction. The mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was successively washed with 1 M HCl, saturated $NaHCO_3$, brine, and then dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1/1) afforded trifluoroacetamide (1.3 g, 100%) as a colorless oil. ^{1}H NMR spectral and HRMS data were completely coincided with those in the literature;[6g] ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.89, 154.69, 149.59, 149.46, 148.15, 148.13, 136.58, 136.52, 129.75, 129.70, 129.63, 128.88, 128.55, 128.46, 127.95, 127.84, 127.63, 127.27, 127.21, 126.70, 121.24, 120.65, 115.60, 115.44, 113.96, 113.41, 111.74, 111.66, 71.01, 70.84, 55.96, 55.93, 51.13, 49.40, 48.22, 48.19, 48.11, 34.14, 31.73; IR ($CHCl_3$): 1686, 1516 cm^{-1}. To a solution of the trifluoroacetamide (1.2 g, 2.5 mmol) in CF_3CH_2OH (12 mL), was added a solution of phenyliodine(III) bis(trifluoroacetate) (1.2 g, 2.8 mmol) in CF_3CH_2OH (12 mL) at −25 °C. The reaction mixture was stirred for 30 min, and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **11** (0.9 g, 78%) as an amorphous powder. ^{1}H NMR, IR spectral and HRMS data were completely coincided with those in the literature;[6g] ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.23, 185.09, 152.88, 152.46, 149.34, 149.20, 147.40, 147.14, 136.43, 136.37, 128.58, 128.53, 128.42, 128.33, 128.01, 127.98, 127.91, 127.67, 127.38, 127.26, 127.16, 127.10, 116.48, 115.91, 113.32, 113.26, 71.12, 70.94, 56.10, 55.97, 48.63, 48.42, 48.28, 48.14, 45.30, 45.27, 44.17, 35.81, 33.83.

4.2.3. 8-Demethyl-3-oxomaritidine (12). Boron trichloride (0.78 mL, 1.0 M solution in dichloromethane, 0.78 mmol) was added to a solution of **11** (238 mg, 0.52 mmol) in dichloromethane (3 mL) at −78 °C. The reaction mixture was stirred for 3 days at −78 °C, and then water was added to quench the reaction. The mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/3) afforded a debenzylated compound (150.9 mg, 79%) as a colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J=10.3 Hz, 1H), 6.95 (d, J=10.3 Hz, 1H), 6.90 and 6.74 (s, 1H), 6.51 (s, 1H), 6.33 (d, J=6.2 Hz, 1H), 6.31 (d, J=6.2 Hz, 1H), 5.76 (brs, 1H, OH), 4.77 and 4.74 (s, 2H), 3.86 (dd, J=12.5, 8.1 Hz, 2H), 3.76 and 3.75 (s, 3H), 2.44–2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.39, 185.26, 153.15, 152.76, 146.33, 144.92, 144.90, 128.63, 128.50, 127.15, 127.01, 117.61, 117.53, 116.31, 112.02, 111.94, 55.97, 55.91, 48.51, 48.22 48.13, 45.34, 45.30, 44.23, 35.83, 33.89; IR ($CHCl_3$): 3541, 1690, 1665, 1626, 1591, 1516 cm^{-1}; HRMS calcd for $C_{18}H_{16}NO_4F_3$ (M^+): 367.1031, found: 367.1034. To a solution of the debenzylated compound (25 mg, 0.07 mmol) in methanol (0.5 mL), was added 10% aqueous solution of potassium hydroxide (0.5 mL) and stirred for 30 min at room temperature. The reaction mixture was concentrated in vacuo and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **12** (16.1 mg, 87%) as colorless crystals; mp 252–255 °C (decomp.) (*n*-hexane) (lit.,[6a,c] mp 250–252 °C, decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J=10.3 Hz, 1H), 6.88 (s, 1H), 6.61 (s, 1H), 6.11 (d, J=10.3 Hz, 1H), 4.40 (d, J=16.8 Hz, 1H), 3.92 (s, 3H), 3.81 (d, J=16.8 Hz, 1H), 3.67 (dd, J=12.9, 5.6 Hz, 1H), 3.56 (ddd, J=13.3, 10.1, 3.5 Hz, 1H), 3.03 (ddd, J=14.2, 7.9, 5.3 Hz, 1H), 2.71 (dd, J=16.8, 5.7 Hz, 1H), 2.49 (dd, J=16.8, 13.0 Hz, 1H), 2.40 (ddd, J=12.4, 9.0, 3.7 Hz, 1H), 2.19 (ddd, J=12.1, 10.5, 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.17, 149.56, 145.29, 144.59, 134.17, 128.74, 125.78, 113.26, 104.53, 68.94, 61.32, 56.10, 54.05, 44.77, 44.46, 40.12; IR ($CHCl_3$): 3543, 1680, 1506 cm^{-1}; HRMS calcd for $C_{16}H_{17}NO_3$ (M^+): 271.1208, found: 271.1205.

4.2.4. Siculine (4). Lithium tri-*sec*-buthylborohydride (L-Selectride®) (0.22 mL, 1.0 M solution in THF, 0.22 mmol) was added to a solution of **12** (24.4 mg, 0.09 mmol) in THF (5 mL) at −78 °C, and the reaction mixture was stirred for 1 day at −78 °C. After quenching the reaction with aqueous solution of Na_2SO_4, the mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded siculine (**4**) (13.1 mg, 53%) as colorless crystals. ^{1}H NMR spectral and EI-MS data were completely coincided with those in the literature;[9] mp 235–239 °C (decomp.) (chloroform); ^{13}C NMR (100 MHz, CD_3OD): δ 148.32, 146.79, 135.70, 133.08, 129.11, 128.07, 122.28, 114.75, 107.36, 68.23, 67.45, 60.99, 56.61, 53.56, 44.38, 33.93; IR ($CHCl_3$): 3331, 2963, 2934, 1506, 1466, 1447, 1315, 1275, 1240, 1198, 1128, 1094, 1026, 868 cm^{-1}; HRMS calcd for $C_{16}H_{19}NO_3$ (M^+): 273.1365, found: 273.1370.

4.2.5. *N*-Trifluoroacetyl-*N*-3′, 4′-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (14a). Tyramine (1.1 g, 8.0 mmol) was added to a solution of piperonal (**13**) (1.0 g, 6.7 mmol) in methanol (8 mL), and the reaction mixture was stirred for 6 h at room temperature.

Sodium borohydride (277.3 mg, 7.3 mmol) was added to the mixture and stirred for 1 day. The reaction mixture was concentrated in vacuo, and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo and treated for further reaction without purification. Trifluoroacetic anhydride (2.4 mL, 16.8 mmol) was added to a solution of the residue in pyridine (18 mL) and the mixture was stirred for 2 h at 0 °C. After quenching the reaction with methanol, the mixture was concentrated in vacuo and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 2/1) afforded **14a** (3.0 g, 100%) as colorless crystals. All the spectral data was coincided with those in the literature.[23]

4.2.6. *N*-Formyl-*N*-3′,4′-methylenedioxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (14b). Tyramine (2.2 g, 16.0 mmol) was added to a solution of piperonal (**13**) (2.0 g, 13.3 mmol) in methanol (32 mL) and the mixture was stirred at room temperature for 3 h. Sodium borohydride (553.4 mg, 14.6 mmol) was added and stirred for 1 h at room temperature. After the reaction, the mixture was concentrated in vacuo, and extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo and treated for further reaction without purification. The residue was dissolved in ethyl formate (40 mL) and refluxed for 2 days, and the mixture was concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 30/1) afforded **14b** (4.3 g, 100%) as colorless crystals; mp 113–115 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 and 7.80 (s, 1H), 7.01 (d, J=8.4 Hz, 1H), 6.92 (d, J=8.4 Hz, 1H), 6.78–6.71 (m, 4H), 6.63 and 6.61 (s, 2H), 4.46 (s, 1H), 4.15 (s, 1H), 3.43 (t, J=7.4 Hz, 1H), 3.33 (t, J=6.5 Hz, 1H), 2.72 (t, J=7.0 Hz, 1H), 2.70 (t, J=6.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.35, 162.91, 155.34, 154.89, 148.24, 148.05, 147.57, 147.21, 129.90, 129.85, 129.35, 128.80, 121.81, 121.18, 115.73, 115.43, 108.77, 108.41, 108.24, 107.86, 101.28, 101.12, 51.68, 48.58, 45.34, 43.58, 33.71, 32.33; IR ($CHCl_3$): 1665, 1516, 1504 cm^{-1}; HRMS calcd for $C_{17}H_{17}NO_4$ (M^+): 299.1157, found: 299.1153. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.30; H, 5.77; N, 4.71.

PIFA oxidation of **14a**. Phenyliodine(III) bis(trifluoroacetate) (64 mg, 0.15 mmol) in CF_3CH_2OH (2 mL) was added to a solution of **14a** (50 mg, 0.14 mmol) in CF_3CH_2OH (3 mL) at −40 °C. The reaction mixture was stirred for 20 min at −40 °C, and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, *n*-hexane/ethyl acetate, 1/1) afforded **15a** (36.9 mg, 74%) as a colorless crystals. All the spectral data was coincided with those in the literature.[6g]

PIFA oxidation of **14b**. Phenyliodine(III) bis(trifluoroacetate) (790.2 mg, 1.8 mmol) in CF_3CH_2OH (10 mL) was added to a solution of **14b** (0.5 g, 1.7 mmol) in CF_3CH_2OH (20 mL) at 0 °C. The reaction mixture was stirred for 30 min and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 20/1) afforded **15b** (0.45 g, 91%) as colorless crystals; mp 195–198 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 and 8.18 (s, 1H), 7.03 (d, J=10.3 Hz, 1H), 6.95 (d, J=10.3 Hz, 1H), 6.80 and 6.65 (s, 1H), 6.56 and 6.54 (s, 1H), 6.32–6.27 (m, 2H), 5.95 and 5.92 (s, 2H), 4.56 and 4.60 (s, 2H), 3.79 and 3.74 (t, J=6.1 Hz, 2H), 2.36–2.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.30, 185.18, 162.60, 161.56, 153.05, 152.46, 147.61, 147.41, 147.06, 147.02, 130.85, 130.75, 129.52, 129.45, 127.24, 127.03, 110.87, 110.18, 109.58, 109.26, 101.73, 101.60, 49.93, 48.50, 48.40, 45.62, 45.30, 40.33, 36.06, 34.23; IR ($CHCl_3$): 1666, 1626, 1506 cm^{-1}; HRMS calcd for $C_{17}H_{15}NO_4$ (M^+): 297.1001, found: 297.1006. Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.41; H, 5.07; N, 4.63.

4.2.7. Oxocrinine (5) from 15a. 10% aqueous solution of potassium hydroxide (1.5 mL) was added to a solution of **15a** (110 mg, 0.30 mmol) in methanol (1.5 mL) at room temperature. The reaction mixture was stirred for 9 h at room temperature, and then concentrated in vacuo. The residue was extracted with chloroform and the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **5** (70.6 mg, 87%) as colorless crystals, accompanied with the starting material **15a** (7.0 mg, 6%). Mp 171–173 °C (ethyl acetate) (lit.,[16a] mp 175–178 °C; lit.,[16b] 170–172 °C). All the spectral data of **5** was completely coincided with those in the literature.[10,16]

4.2.8. Preparation of oxocrine (5) from 15b. 10% aqueous solution of potassium hydroxide (1.0 mL) was added to a solution of **15b** (45.5 mg, 0.15 mmol) in methanol (1.5 mL) at room temperature. The reaction mixture was stirred for 9 h at 60 °C, and then concentrated in vacuo. The residue was extracted with chloroform and the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **5** (25.3 mg, 61%) as colorless crystals. All the spectral data of **5** was completely coincided with those in the literature.[10,16]

4.2.9. Epicrinine (6). Lithium tri-*sec*-buthylborohydride (L-Selectride®) (0.37 mL, 1.0 M solution in THF, 0.37 mmol) was added to a solution of **5** (42 mg, 0.16 mmol) in THF (1 mL) at −78 °C, and the reaction mixture was stirred for 1 day at −78 °C. The reaction was quenched with saturated aqueous Na_2SO_4, and the mixture was extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded epicrinine (**6**) (34.6 mg, 82%) as colorless crystals. Mp 232–235 °C (decomp.) (ethyl acetate) (lit.,[16a] mp 235–239 °C; lit.,[18] 234–235 °C). All the spectral data was coincided with those in the literature.[11,17]

4.2.10. *N*-Formyl-*N*-3′,4′-dimethoxyphenylmethyl-[2-(4-hydroxyphenyl)]ethylamine (17). Tyramine (990.6 mg, 7.22 mmol) was added to a solution of 3,4-dimethoxybenzaldehyde (**16**) (1.0 g, 6.02 mmol) in methanol (12 mL), and the reaction was stirred for 6 h at room temperature. Sodium borohydride (250.5 mg, 6.62 mmol) was added to the mixture, and it was stirred for 4 h at room temperature

and concentrated in vacuo. The residue was extracted with chloroform and the organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo, and treated for further reaction without purification. The residue was dissolved in ethyl formate (30 mL) and refluxed for 1 day, and then concentrated in vacuo. Crystallization of the residue from diethyl ether afforded **17** (1.82 g, 96%) as colorless crystals; mp 95–97 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 and 7.81 (s, 1H), 6.99 (d, J=8.6 Hz, 1H), 6.89 (d, J=8.6 Hz, 1H), 6.84–6.61 (m, 5H), 4.50 and 4.20 (s, 2H), 3.869 and 3.866 (s, 3H), 3.84 and 3.83 (s, 3H), 3.45 and 3.34 (t, J=6.9 Hz, 2H), 2.71 and 2.70 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.39, 163.01, 155.51, 155.13, 149.29, 149.21, 148.90, 149.61, 129.78, 129.69, 129.55, 128.59, 127.86, 120.82, 120.15, 115.68, 115.41, 111.46, 111.18, 110.93, 110.41, 55.88, 55.83, 51.70, 48.69, 45.45, 43.65, 33.68, 32.33; IR ($CHCl_3$): 1663, 1614, 1595 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_4$ (M^+): 315.1470, found: 315.1465. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.70; H, 6.70; N, 4.59.

PIFA oxidation of **17**. Phenyliodine(III) bis(trifluoroacetate) (1.5 g, 3.49 mmol) in CF_3CH_2OH (10 mL) was added to a solution of **17** (1.0 g, 3.17 mmol) in CF_3CH_2OH (20 mL). The reaction mixture was stirred for 30 min at room temperature, and then concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 50/1) afforded **18** (912.8 mg, 92%) as colorless crystals; mp 187–189 °C (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 and 8.20 (s, 1H), 7.09 and 6.99 (d, J=10.2 Hz, 2H), 6.82 and 6.66 (s, 1H), 6.54 and 6.53 (s, 1H), 6.32 and 6.31 (d, J=10.2 Hz, 2H), 4.12 and 4.65 (s, 2H), 3.891 and 3.885 (s, 3H), 3.82 and 3.77 (t, J=6.2 Hz, 2H), 3.734 and 3.731 (s, 3H), 2.38–2.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.40, 185.28, 162.57, 161.53, 153.25, 152.66, 148.30, 148.05, 147.99, 147.97, 129.62, 129.51, 128.10, 127.97, 127.11, 126.89, 113.64, 113.01, 112.62, 112.25, 55.93, 55.91, 55.87, 49.83, 48.39, 48.26, 45.65, 45.15, 40.31, 36.24, 34.38; IR ($CHCl_3$): 1666, 1624, 1609, 1522 cm^{-1}; HRMS calcd for $C_{18}H_{19}NO_4$ (M^+): 313.1314, found: 313.1317. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.71; H, 6.12; N, 4.60.

4.2.11. Dienone–phenol rearrangement of 18. Methanesulfonic acid (1.5 mL) was added to **18** (50 mg, 0.16 mmol) at room temperature, and stirred for 1 day. The mixture was neutralized with saturated aqueous $NaHCO_3$, and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, ethyl acetate) afforded **19** (45.9 mg, 92%) as colorless crystals; mp 229–231 °C (methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 and 8.12 (s, 1H), 7.33 (s, 1H), 7.14 and 7.11 (d, J=8.2 Hz, 1H), 6.91 and 6.88 (d, J=2.6 Hz, 1H), 6.83 and 6.80 (d, J=2.7 Hz, 1H), 6.82 and 6.77 (s, 1H), 6.47 and 6.45 (brs, 1H, OH), 5.11 and 5.07 (s, 1H), 3.93 and 3.89 (s, 3H), 3.88 and 3.86 (s, 3H), 3.84–3.81 (m, 1H), 3.22 and 3.19 (d, J=10.9, 1H), 3.22 and 3.18 (s, 1H), 2.91 and 2.88 (d, J=6.4 Hz, 1H), 2.35 and 2.32 (d, J=11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.57, 162.07, 154.73, 148.62, 148.13, 141.36, 140.91, 132.54, 131.11, 130.66, 128.03, 127.87, 116.50, 116.06, 115.47, 115.29, 113.62, 112.38, 111.81, 111.42, 60.49, 55.94, 55.92, 50.18, 49.85, 44.55, 43.17, 34.32, 32.41; IR ($CHCl_3$): 1659, 1607, 1578, 1518 cm^{-1}, HRMS calcd for $C_{18}H_{19}NO_4$ (M^+): 313.1314, found: 313.1318. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.71; H, 6.12; N, 4.42.

4.2.12. *N*-Formyl-2,3-dimethoxy-10-trifluoromethanesulfonyloxy-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (20). Trifluoromethanesulfonic anhydride (0.065 mL, 0.38 mmol) was added to a solution of **19** (50 mg, 0.16 mmol) in pyridine (1 mL) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C and then continued to stir for another 3 h at room temperature. The reaction was quenched with water and the mixture was extracted with ethyl acetate. The organic layer was washed with 1 M HCl, saturated $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 10/1) afforded **20** (44.9 mg, 63%) as colorless crystals, accompanied with the starting material **19** (17 mg, 34%); mp 124–125 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 and 8.13 (s, 1H), 7.41–7.25 (m, 4H), 6.76 and 6.73 (s, 1H), 5.16 and 5.13 (s, 1H), 3.95 (s, 3H), 3.93 (m, 1H), 3.92 and 3.91 (s, 3H), 3.25 and 3.22 (d, J=10.8 Hz, 1H), 3.11 and 3.08 (s, 1H), 3.03 and 3.00 (d, J=6.6 Hz, 1H), 2.45 and 2.41 (dd, J=11.1, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.23, 161.75, 149.56, 149.34, 148.99, 148.41, 147.83, 147.75, 142.61, 142.10, 140.48, 139.73, 131.38, 131.27, 130.87, 130.48, 128.44, 128.29, 122.46, 122.09, 120.90, 120.73, 120.32, 117.13, 113.94, 112.23, 111.64, 111.57, 56.11, 56.07, 56.01, 50.03, 48.88, 44.39, 42.30, 34.83, 32.96; IR ($CHCl_3$): 1665, 1607, 1574, 1518 cm^{-1}; HRMS calcd for $C_{19}H_{18}NO_4SF_3$ (M^+): 445.0807, found: 445.0804. Anal. Calcd for $C_{19}H_{18}NO_4SF_3$: C, 51.23; H, 4.07; N, 3.14. Found: C, 51.49; H, 4.25; N, 3.12.

4.2.13. *N*-Formyl-2,3-dimethoxy-5,6,7,8-tetrahydrodibenz-[*c*,*e*]azocine (21). Palladium acetate (4.3 mg, 0.019 mmol), triphenylphosphine (10.1 mg, 0.039 mmol), formic acid (0.007 mL, 0.193 mmol) and triethylamine (0.041 mL, 0.291 mmol) were added to a solution of **20** (43.0 mg, 0.097 mmol) in *N*,*N*-dimethylformamide (1 mL), and then the reaction mixture was stirred for 2 days at 60 °C. The mixture was concentrated in vacuo and the residue was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded **21** (25.0 mg, 87%) as colorless crystals; mp 185–187 °C (methanol); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 and 8.13 (s, 1H), 7.40–7.26 (m, 5H), 6.79 (s, 1H), 5.13 and 5.10 (s, 1H), 3.95 (s, 3H), 3.91–3.86 (m, 1H), 3.90 and 3.89 (s, 3H), 3.26 and 3.22 (d, J=11.1 Hz, 1) 3.16 and 3.12 (s, 1H), 2.98 and 2.95 (d, J=6.6 Hz, 1H), 2.44 and 2.40 (dd, J=11.0, 1.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.25, 161.76, 148.81, 148.68, 148.56, 148.08, 140.13, 139.98, 139.68, 139.18, 132.98, 132.54, 129.82, 129.49, 129.40, 128.35, 128.33, 128.18, 128.13, 126.74, 126.60, 113.64, 112.44, 111.87, 111.41, 56.02, 55.95, 55.88, 49.99, 49.29, 44.39, 42.66, 35.25, 33.37; IR ($CHCl_3$): 1661, 1607, 1518 cm^{-1}; HRMS calcd for $C_{18}H_{19}NO_3$ (M^+): 297.1365, found: 297.1361. Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.70; H, 6.35; N, 4.74.

4.2.14. Buflavine (7). A suspension of $LiAlH_4$ (4.5 mg, 0.12 mmol) in THF was added to a solution of **21** (23.4 mg, 0.08 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 15 h at room temperature, and then the reaction was quenched with saturated solution of Na_2SO_4, extracted with chloroform. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (silica gel, chloroform/methanol, 5/1) afforded **7** (21.1 mg, 94%) as a viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.22 (m, 4H), 6.91 (s, 1H), 6.80 (s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.54 (d, J=13.6 Hz, 1H), 3.27 (t, J=9.3 Hz, 1H), 3.08 (d, J=13.6 Hz, 1H), 2.77–2.66 (m, 1H), 2.60–2.49 (m, 2H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.41, 147.89, 141.22, 140.00, 132.96, 132.35, 129.65, 129.44, 129.02, 127.88, 126.08, 113.58, 112.14, 58.65, 58.29, 55.93, 45.82, 32.49; IR ($CHCl_3$): 1607, 1522 cm^{-1}; HRMS calcd for $C_{18}H_{21}NO_2$ (M^+): 283.1572, found: 283.1566.

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Synthesis of dihydropyrazolo[3′,4′:3,4]pyrrolo[1,2-a]indoles and spiro-[3*H*-indole-3,3′-[Δ²-1,2,4]-triazolin]-2-ones via intra and intermolecular 1,3-dipolar cycloadditions

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Abstract—A new class of dihydropyrazolo[3′,4′:3,4]pyrrolo[1,2-a]indoles and spiro[3*H*-indole-3,3′-[Δ^2-1,2,4]-triazoline]-2-ones were synthesised via intra and intermolecular 1,3-dipolar cycloaddition reactions in good yields.

1. Introduction

The potent antitumour antibiotic mitomycins[1] have attracted a great deal of interest and a variety of molecular manipulations have been reported without loss of any significant biological activities.[2] Indeed mitomycin C is a clinically useful chemotherapeutic agent for the treatment of various tumors. Although numerous C_1-fused furan, thiophene and pyridine annelated mitomycins are reported, they have their limitations due to the fact that these heterocycles are not prone to ring transformations.[3] The indole nucleous annulated to carbocyclic or heterocyclic ring(s) is present in an astonishing variety of natural products endowed with potent and multiform biological activities.[4] Hence, new and efficient syntheses of such compounds is still important. Several syntheses of mitomycin analogues and other mitosenes have been reported.[5] Access to the pyrrolo[1,2-a]indole skeleton which is common for these compounds is generally carried out by radical cyclizations,[6] metal carbene insertions,[7] or intramolecular cyclizations.[8] The dihydropyrazoles have rich chemistry because of their ready reductive cleavage[9] and susceptibility to ring transformations.[10] We envisioned[11] the construction of a functionalised ring annulated to the 1,2-position of the indole nucleus using a cycloaddition strategy. Undoubtedly, intramolecular cycloaddition reactions have emerged as the single most powerful methodology for the construction of bicyclic and polycyclic ring systems.[12] Our approaches to the synthesis of these target molecules involves intramolecular nitrile imine cycloaddition reactions.

Keywords: Intramolecular cycloaddition; Spiroindoles; Dihydropyrazolopyrrolo indoles; Triazolines; Intermolecular cycloaddition.
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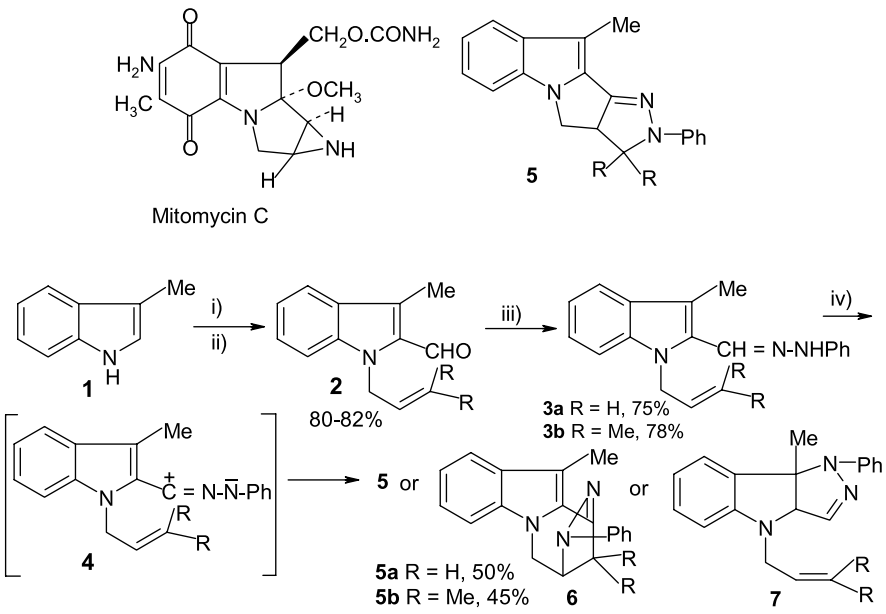
2. Results and discussion

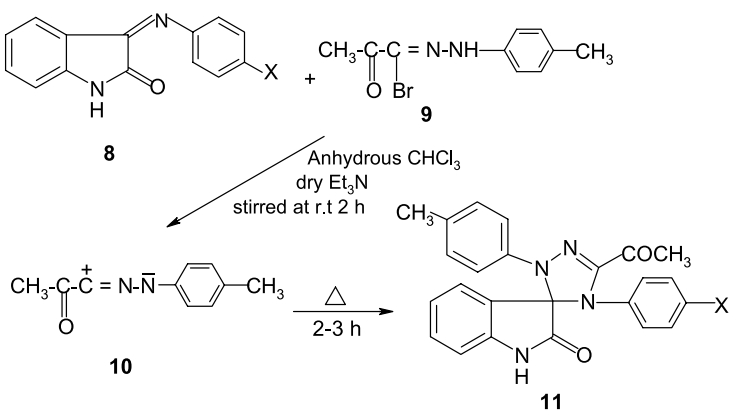
2-Formyl-3-methyl-N-allyl indoles **2** were obtained from 3-methylindole by condensation with allyl bromide under phase transfer conditions followed by in situ Vilsmeier–Haack reactions (80–82%).[13] The aldehydes **2** were further converted into their corresponding phenylhydrazones **3** in 75–78% yields by reaction with phenylhydrazine hydrochloride and sodium acetate in ethanol. Three typical methods for bromination of hydrazones **3**, namely N-bromosuccinimide (NBS) in CCl_4, Lee's method (sodium hypochlorite in sodium hydroxide solution) and NBS in DMF at low temperature (0–10 °C), were not successful (TLC showed a large number of products formed). Therefore, the nitrile imine intermediate was generated in situ by oxidation of the hydrazone **3** with lead tetraacetate in dry acetonitrile at −15 °C, which underwent intramolecular 1,3-dipolar cycloaddition with the alkene to provide 9-methyl-1-phenyl-dihydropyrazolo[3′,4′-3,4]pyrrolo[1,2-a]indole **5a** in 50% yield, without the formation of any strained bridged-ring adduct **6** or cyclized product **7**. Since the NMR spectra of the cycloadduct **5a** showed no signals typical of the allyl group, it is clear that the allylic double bond had taken part in the cycloaddition. The elemental analysis of the cycloadduct **5a** also gave satisfactory results. To further investigate the synthetic scope of this intramolecular cycloaddition strategy 4-bromo-2-methyl-but-2-ene was converted in a similar way to the corresponding cycloadduct **5b** (R=Me), isolated in 45% yield. A similar strategy has been used by Moody et al., who have synthesized various cyclopropapyrrolo[1,2-a]indole and pyrazolino indoles based on intramolecular 1,3-dipolar cycloaddition strategy.[14] In their work, the indole-2-carboxaldehyde was treated with sodium hydride in DMF followed by the appropriate allylbromide to get the corresponding *N*-allyl



Scheme 1. (i) Allylbromide, PTC; (ii) DMF/$POCl_3$; (iii) $PhNHNH_2$·HCl/CH_3COONa; (iv) $Pb(OAc)_4$/MeCN.

derivatives. This was further converted into tosylhydrazones by reaction with toluene-*p*-sulfonylhydrazide in methanol. Finally, thermolysis of the sodium salt of the tosylhydrazone in boiling chlorobenzene afforded cyclopropapyrroloindole in 27% yield. When the sodium salt was decomposed at a lower temperature in boiling benzene, the [3+2] cycloadduct, pyrrolinoindole, was obtained in 29% yield with the loss of the arylsulfonyl group. In contrast, we have performed the intramolecular dipolar cycloaddition of 3-methylindole in a much simpler way and obtained the corresponding pyrazolopyrroloindoles in 50% yield without loss of any diazo or arylsulfonyl group (Scheme 1).

In recent years, a systematic study of spiroindole has been carried out due to the increased spectrum of their biological activities.[15] The indole ring, linked to other heterocyclic system through the spiro carbon atom at C-3, are of interest. In addition, varied pharmacological properties are associated with 1,2,4-triazolines.[16] Thus, it is possible that production of a 1,2,4-triazoline moiety at the C-3 position of the indolinone system could enhance biological activity. We have investigated a facile synthesis of triazolines with a new skeleton **11** in high yields under thermal conditions. Nitrile imines are important intermediates[17] as 1,3-dipoles, investigated by many research groups.[18,19] Diphenyl nitrile imines, are less reactive in comparison to their non-aromatic counterpart, C-acetyl[20] and C-ethoxycarbonyl nitrile imines[21] but they have been more systematically investigated. The reaction of these dipoles with non-conjugated[22] and conjugated imines[23] have been well-studied. The reaction with isatin imines, which is the subject of this study, does not appear to have been previously investigated. Spiro-[3*H*-indole-3,3′-[Δ^2-1-2-4]-triazoline]-2-ones **11** were obtained by the reaction of isatin imines[24] **8** with C-acetyl nitrile imine **10**, generated in situ from the corresponding hydrazinoyl bromide **9**. The reaction time was generally between 4–5 h and the yield was good to excellent. Furthermore, there were no side products formed (Scheme 2). The structure of compounds **11a–e** thus obtained were confirmed on the basis of their IR, ^1H NMR and mass spectral analyses. In the IR spectra $\nu_{C=O}$ of



Scheme 2.

the oxindole appear at 1729–1750 cm^{-1}, $\nu_{C=O}$ of the acetyl at 1660–1679 cm^{-1} and ν_{N-H} at 3253–3337 cm^{-1}. The ^1H NMR spectra of products **11a–e** showed the corresponding resonance peaks as a singlet of methyl, carbomethoxy and N–H groups, at δ_H=2.1–2.2, δ_H=2.5–2.6 and δ_H=8.1–8.2 ppm, respectively.

Entry	X	Product	Yield (%)
1	H	**11a**	80
2	CH_3	**11b**	82
3	OCH_3	**11c**	80
4	Cl	**11d**	70
5	Br	**11e**	65

3. Conclusion

In conclusion, we have demonstrated that a 1,3-dipole (nitrile imine) generated in situ from the corresponding hydrazone oxidatively undergoes intramolecular 1,3-dipolar cycloaddition onto the alkene of an allyl-substituted indole. The dihydropyrazoloindoles and spiroindoles possessing suitable heterocycles have potential as precursors to various mitomycin analogues.

4. Experimental

Materials were obtained from commercial suppliers and were used without further purification. Melting points were determined by using a Buchi melting point apparatus and are uncorrected. IR spectra were recorded for KBr discs on a Perkin–Elmer 240C analyser. ^1H NMR spectra were recorded on 90 MHz spectrometers and chemical shift values are recorded in δ units (ppm) relative to Me_4Si as internal standard. The 270 and 100 MHz NMR spectra were recorded with tetramethylsilane as internal standard (by RSIC, Shillong). Mass spectra were recorded in an AEIMS-30 spectrometer. Elemental analyses were performed on a Hitachi 026 CHN analyser. All solvents were distilled before use. The progress of most reactions was monitored by TLC and chromatographic purification was performed with silica gel 60 (120 mesh, Merck).

4.1. General procedure for the preparation of hydrazones 3

4.1.1. 1-Allyl-3-methylindole-2-carbaldehyde phenylhydrazone 3a. A solution of 2-formyl-3-methyl-*N*-allylindole **2a** (1.99 g, 10 mmol) in ethanol (25 mL) was added dropwise to a well stirred solution of phenylhydrazine hydrochloride (1.44 g, 10 mmol) and sodium acetate (2.05 g, 25 mmol) in water (10 mL). The stirring was continued for 10–15 min after which the reaction mixture was warmed on a water bath for 15 min. The precipitated hydrazone was filtered off, washed with water, dried and recrystallised from ethanol. Concentration of the mother liquor gave additional (10%) hydrazone **3a**. The total yield was 2.45 g (75%). Yellowish solid. Mp 162–165 °C (decomp.). [Found: C, 78.98; H, 6.63; N, 14.44. $C_{19}H_{19}N_3$ requires C, 78.89; H, 6.57; N, 14.53%]. ν_{max} (Nujol) 3210, 1615, 1320, 1160 and 745 cm^{-1}. δ_H (90 MHz, $CDCl_3$) 8.10 (broad, 1H, –NH), 7.18–7.42 (m, 9H, ArH), 6.75 (s, 1H, CH=N), 5.62–6.14 (m, 1H, CH=CH_2), 4.84–5.20 (m, 3H, NCH_2, =CH H), 4.66–4.76 (m, 1H, =CH H) and 2.44 (s, 3H, Me). EI-MS: *m/z* 289 (M^+).

4.1.2. 1-(2-Methylbut-2-enyl)-3-methylindole-2-carbaldehyde phenylhydrazone 3b. Following the above procedure, 1-(2-methylbut-2-enyl)-3-methylindole-2-carbaldehyde **2b** (2.25 g, 10 mmol), with phenylhydrazine hydrochloride (1.44 g, 10 mmol) and sodium acetate (2.05 g, 25 mmol) in ethanol-water gave the title compound **3b** in 78% (2.75 g) yield as a yellowish solid. Mp 170–172 °C (decomp.). [Found: C, 79.61; H, 7.32; N, 13.36. $C_{21}H_{23}N_3$ requires C, 79.49; H, 7.25; N, 13.25%]. ν_{max} (KBr) 3200, 1610, 1350, 1165, 1050 and 670 cm^{-1}. δ_H (90 MHz, $CDCl_3$) 7.62 (br, 1H, NH), 7.10–7.26 (m, 9H, ArH), 6.72 (s, 1H, CH=N), 5.12 (s, 3H, NCH_2CH), 2.36 (s, 3H, Me), 1.86 (s, 3H, Me), 1.64 (s, 3H, Me). EI-MS: *m/z* 317 (M^+).

4.1.3. 9-Methyl-1-phenyl-dihydropyrazolo [3′,4′:3,4]-pyrrolo[1,2-a]indole 5a. A solution of lead tetraacetate (2.30 g, 5.2 mmol) in dry acetonitrile (30 mL) was added dropwise to a stirred and cooled solution of 1-allyl-3-methylindole-2-carbaldehyde phenylhydrazone **3a** (1.01 g, 3.48 mmol) in dry acetonitrile (100 mL) at −15 °C during 1 h, after which the reaction mixture was set aside at the same temperature. The resultant precipitate was filtered off and filtrate was evaporated to dryness. The residue thus obtained was poured into water and extracted with dichloromethane (50 mL×3). The combined organic extracts were washed with water several times, dried and distilled in a rotary evaporator to afford a residue, which on crystallization from ethanol gave 9-methyl-1-phenyl-dihydropyrazolo[3′,4′:33,4] pyrrolo[1,2-a]indole **5a** in 50% yield (0.5 g) as pale yellow needles. Mp 182–184 °C. [Found: C, 79.29; H, 5.88; N, 14.58. $C_{19}H_{17}N_3$ requires C, 79.40; H, 5.96; N, 14.62%]. δ_H (270 MHz, $CDCl_3$) 1.98 (s, 3H), 3.90 (dd, *J*=3.9, 10.3 Hz 1H), 4.01–4.10 (m, 1H), 4.13 (dd, *J*=10.3, 3.2 Hz, 1H), 4.31 (dd, *J*=10.3, 8.1 Hz, 1H), 4.78 (br, s, 1H), 7.12 (t, *J*=7.2 Hz, 1H), 7.25 (t, *J*=7.0 Hz, 1H), 7.32–7.50 (overlapping, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) 21.1, 48.7, 50.8, 62.6, 94.9, 109.7, 119.6, 121.2, 125.8, 127.5, 128.5, 129.1, 130.5, 133.5, 137.1, 142.0, 147.1. EI-MS: *m/z* 287 (M^+).

4.1.4. 9-Methyl-1-phenyl-2,2′-dimethyl-dihydropyrazolo [3′,4′:3,4]pyrrolo[1,2-a]indole 5b. Following the above procedure, 1-(2-methylbut-2-enyl)-3-methylindole-2-carbaldehyde phenyl hydrazone **3b** (1.10 g, 3.5 mmol) with lead tetraacetate (2.3 g, 5.2 mmol) in dry acetonitrile at −15 °C gave the title compound **5b** in 45% yield (0.46 g) as a pale yellow solid. Mp 124–126 °C. [Found: C, 79.89; H, 6.63; N, 13.46. $C_{21}H_{21}N_3$ requires C, 79.96; H, 6.71; N, 13.32%]. δ_H (270 MHz, $CDCl_3$) 1.16 (s, 3H), 1.33 (s, 3H), 2.21 (s, 3H), 4.20 (dd, *J*=10.3, 2.9 Hz, 1H), 4.36 (dd, *J*=10.3, 8.1 Hz, 1H), 4.11 (m, 1H), 7.22 (t, *J*=7.3 Hz, 1H), 7.34 (t, *J*=7.1 Hz, 1H), 7.37–7.52 (overlapping, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) 12.5, 19.7, 21.6, 49.7, 50.9, 63.1, 95.0, 109.5, 119.6, 121.3, 125.1, 127.6, 128.7, 129.2, 132.9, 133.4, 137.1, 141.2, 148.1. EI-MS: *m/z* 315 (M^+).

4.2. Reaction of hydrazinoyl bromide 9 with isatin imines 8 and synthesis of spiroindoles 11

To a solution of isatinimine **8a** (10 mmol) in anhydrous chloroform (15 mL) was added hydrazinoyl bromide **9** (10 mmol) and stirred well. To this solution, dry triethylamine (15 mmol) dissolved in 10 mL of anhydrous $CHCl_3$ was added dropwise in 40 min. After stirring for 10 min the solution was refluxed with stirring for 3 h and cooled to room temperature (monitored by TLC). The chloroform was then removed under reduced pressure and the residue was treated with dry benzene (20 mL). The precipitated triethylamine hydrobromide was filtered off and the solvent was removed under reduced pressure. The product thus obtained was then purified by column chromatography on silica gel using $CHCl_3$ as eluent and isolated the corresponding cycloadduct **11a** in 80% yield without the formation of any side products. The physical and spectral data of the cycloadduct is recorded below.

4.2.1. Compound 11a. Yellow needles, yield 80% (3.15 g), mp 148–51 °C. [Found: C, 72.62; H, 5.14; N, 14.18. $C_{24}H_{20}N_4O_2$ requires C, 72.72; H, 5.05; N, 14.14%]. ν_{max} (cm^{-1}) 3339 (N–H), 1750 (C═O), 1660 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.25 (bs, 1H, NH), 6.4–7.5 (m, 13H, ArH), 2.5–2.55 (s, 3H, $COCH_3$), 2.18–2.2 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$) 36.2 (CH_3), 41.1 ($COCH_3$), 96.8 (spiro carbon), 111.3, 113.6, 119.5, 122.6, 125.8, 127.7, 128.4, 128.6, 129.7, 130.5, 131.8, 133.0, 141.7, 145.8, 170.03 (C═O), 175.11 (C═O). EI-MS: *m/z* 396 (M^+). Similarly other isatin imines were reacted with hydrazinoyl bromides and the corresponding cycloadducts **11b–e** were isolated in high yields. The physical and spectral data of the spiroindoles are recorded below.

4.2.2. Compound 11b. Yellow needles, yield 82% (3.30 g), mp 188–90 °C. [Found: C, 73.09; H, 5.27; N, 13.63. $C_{25}H_{22}N_4O_2$ requires C, 73.17; H, 5.36; N, 13.65%]. ν_{max} (cm^{-1}) 3363 (N–H), 1739 (C═O), 1660 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.10 (bs, 1H, NH), 6.3–7.3 (m, 12H, ArH), 2.45–2.4 (s, 3H, $COCH_3$), 2.1–2.2 (s, 6H, CH_3); δ_c (100 MHz, $CDCl_3$), 35.9 (CH_3), 36.1 (CH_3), 40.9 ($COCH_3$), 97.02 (spiro carbon), 111.9, 113.1, 118.8, 122.6, 124.8, 127.1, 128.2, 128.9, 129.1, 130.8, 132.1, 133.5, 141.8, 146.1, 147.2, 171.11 (C═O), 175.19 (C═O). EI-MS: *m/z* 410 (M^+).

4.2.3. Compound 11c. Yellow needles, yield 80% (3.45 g), mp 75–77 °C. [Found: C, 70.29; H, 5.25; N, 13.03 $C_{25}H_{22}N_4O_3$ requires C, 70.42; H, 5.16; N, 13.14%]. ν_{max} (cm^{-1}) 3253 (N–H), 1729 (C═O), 1679 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.05–8.15 (bs, 1H, NH), 6.4–7.5 (m, 12H, ArH), 4.6–4.7 (s, 3H, OCH_3), 2.5–2.6 (s, 3H, $COCH_3$), 1.15–1.2 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$), 37.6 (CH_3), 41.2 ($COCH_3$), 60.1 (OCH_3), 96.2 (spiro carbon), 111.5, 113.6, 120.1, 121.8, 124.8, 127.1, 128.1, 128.8, 129.2, 130.5, 131.2, 133.0, 140.8, 146.1, 168.8 (C═O), 172.81 (C═O). EI-MS: *m/z* 426 (M^+).

4.2.4. Compound 11d. Yellow needles, yield 70% (3.0 g), mp 197–99 °C. [Found: C, 66.98; H, 4.33; N, 12.88. $C_{24}H_{19}ClN_4O_2$ requires C, 66.89; H, 4.41; N, 13.00%]. ν_{max} (cm^{-1}) 3337 (N–H), 1742 (C═O), 1660 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 7.8–7.9 (bs, 1H, NH), 6.3–7.3 (m, 12H, ArH), 2.4–2.5 (s, 3H, $COCH_3$), 2.1–2.2 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$), 37.6 (CH_3), 41.2 ($COCH_3$), 97.0 (spiro carbon), 111.1, 112.8, 119.1, 122.6, 124.1, 126.8, 128.0, 128.8, 129.6, 130.8, 132.0, 133.8, 141.1, 146.6, 147.6, 170.0 (C═O), 174.7 (C═O). EO-MS: m/z 430 (M^+).

4.2.5. Compound 11e. Yellow semi solid, yield 65% (3.10 g). [Found: C, 60.53; H, 3.85; N, 11.90 $C_{24}H_{19}BrN_4O_2$ requires C, 60.63; H, 4.00; N, 11.79%]. ν_{max} (cm^{-1}) 3342 (N–H), 1745 (C═O), 1663 ($COCH_3$): δ_H (90 MHz, $CDCl_3$) 8.3 (bs, 1H, NH), 7.75–7.83 (m, 12H, ArH), 2.35–2.5 (s, 3H, $COCH_3$), 2.1–2.15 (s, 3H, CH_3); δ_c (100 MHz, $CDCl_3$), 35.9 (CH_3), 42.5 ($COCH_3$), 96.3 (spiro carbon), 111.8, 113.8, 120.1, 122.8, 125.0, 127.8, 128.1, 128.8, 129.6, 130.6, 131.8, 133.6, 140.8, 145.6, 169.9 (C═O), 174.9 (C═O). EI-MS: *m/z* 474 (M^+).

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Tomato steroidal alkaloid glycosides, esculeosides A and B, from ripe fruits

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Abstract—Major novel steroidal alkaloid glycosides, named esculeoside A (**1**) and esculeoside B (**2**), have been isolated from the pink color-type and the red color-type, respectively, of the ripe tomato fruits of *Lycopersicon esculentum* MILL. for the first time. The structures of **1** and **2** have been characterized as 3-*O*-β-lycotetraosyl (5*S*,22*S*,23*S*,25*S*)-23-acetoxy-3β,27-dihydroxyspirosolane 27-*O*-β-D-glucopyranoside and 3-*O*-β-lycotetraosyl (5*S*,22*S*,23*R*,25*S*)-22,26-epimino-16β,23-epoxy-3β,23,27-trihydroxycholestane 27-*O*-β-D-glucopyranoside, respectively.

1. Introduction

Tomato, the fruit of *Lycopersicon esculentum* MILL., is most widely used as a fresh vegetable and for cooking. The species of tomato in the market is roughly classified into two groups, red color-type and pink color-type; the red color-type tomato is mainly used for pasta sauce and in cooking and the pink color-type tomato as a fresh vegetable. Tomato has received much attention due to the occurrence of lycopene having a strong anti-oxidant activity. With regard to the recent studies on the constituents of tomato, a bitter principle, named TFI,[1] isolated from tomato seeds, steroidal alkaloid glycosides; tomatine[2] and some spirosolane glycosides[3] obtained from the stems and leaves, and lactone,[4] pregnane,[5] and several spirosolane derivatives[6] from the roots of a tomato stock were reported, while it has been regarded that the steroidal alkaloid is not included in the ripe fruit. Now we have isolated a new major spirosolane-type glycoside, named esculeoside A (**1**),[7] from the fruits of Cherry tomato (*L. esculentum* var. *cerasiforme* (DUNAL) ALEF. and the pink color-type tomato (Momotaro), and a novel major solanocapsine-type glycoside, named esculeoside B (**2**), from the red color-type tomato (Italian San Marzano). This paper deals with the first isolation of the tomato steroidal alkaloid glycosides from the ripe fruits, and their structural characterization, and their bioactivities.

Keywords: Tomato: *Lycopersicon esculentum*; Steroidal alkaloid glycoside; Spirosolane-type; Solanocapsine-type; Cytotoxicity; Anti-herpes activity.
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2. Results and discussion

Esculeoside A (**1**), colorless needles, 225 °C (decomp.), $[\alpha]_D$ −52.5° (MeOH), obtained by considerable simple procedure using column chromatographies of Diaion HP-20 (high-porous polystyrene gel), and reversed silica gel in a yield of 440 mg from the methanolic extract of the commercial ripe tomato fruits (1.78 kg) of the Cherry tomato. From the pink color-type, this same compound was also isolated (311 mg from 7.53 kg). Compound **1** has a molecular formula of $C_{58}H_{95}NO_{29}$ based on the HR-FABMS. Two angular methyl signals at δ 0.66 (s), 0.89 (s), one secondary methyl signal at δ 1.07 (d, *J*=6.7 Hz), and one acetyl methyl signal at δ 2.11 (s) together with five anomeric proton signals (each 1H, d, *J*=7.3 Hz, δ 4.88; *J*=7.9 Hz, δ 4.89; *J*=7.9 Hz, δ 5.19; *J*=7.9 Hz, δ 5.23; *J*=7.3 Hz, δ 5.57) were observed in the ^{1}H NMR spectrum (in pyridine-d_5). Since the above evidence suggested **1** to be a steroidal glycoside, **1** was subjected to acid hydrolysis to give a sole sapogenol, designated esculeogenin A (**3**), colorless needles, mp 215–220 °C, $[\alpha]_D$ −99.6° (pyridine) along with sugar components. The EI-MS showed a base peak at *m/z* 447 together with characteristic peaks at *m/z* 170 due to $[C_9H_{16}NO_2]^+$ and *m/z* 146 due to $[C_6H_{12}NO_3]^+$ originated from α-cleavage between C-16-oxygen and C-22, and between C-20 and C-22, respectively, indicating **3** to be a spirosolane-type derivative and the presence two hydroxy groups at F-ring. The ^{1}H NMR signals (in pyridine-d_5) comprised three methyl signals at δ 0.78 (s), 1.01 (s) and 1.08 (d, *J*=6.7 Hz) (Fig. 1). On the other hand, total 27 ^{13}C signals (in pyridine-d_5, Table 1) includes four oxygen-bearing carbons at δ 63.8, 66.0, 70.6, 79.6, one spirosolane

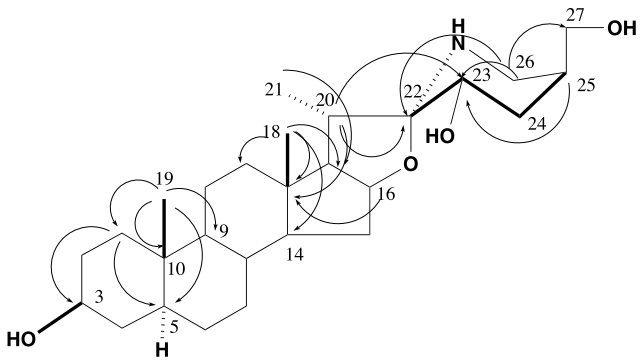


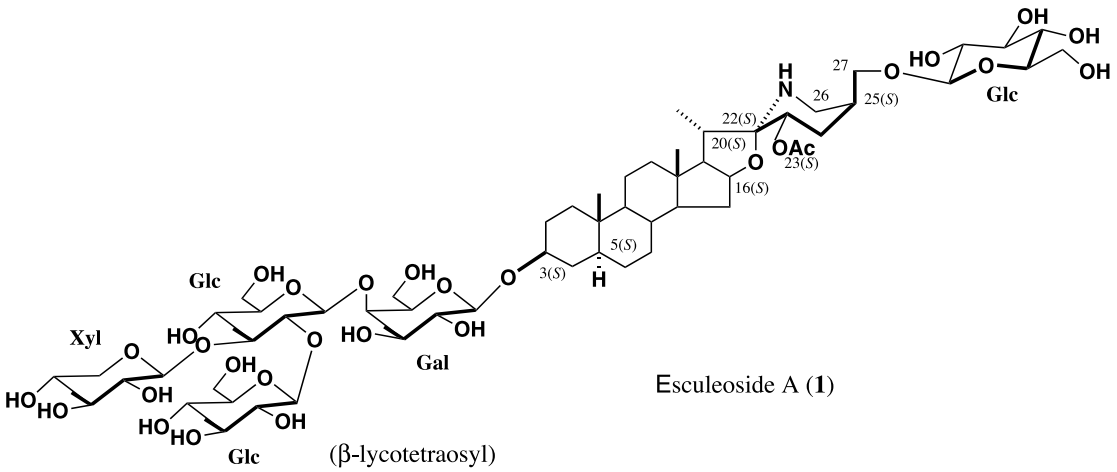
Figure 1. Key HMBC of esculeogenin a (**3**).

center carbon at δ 101.7 and one nitrogen-bearing carbon at δ 40.7. 2D NMR measurements containing FG-COSY, HMQC and HMBC provided the following partial structures: 1) Correlation of H_3-21 (δ_H 1.08)→C-20 (δ_C 35.0)→H-20 (δ_H 3.00)→C-22 (δ_C 101.7) suggested **3** to be a spirosolane derivative; 2) H-20 (δ_H 3.00)→C-23 (δ_C 66.0)→H-25 (δ_H 2.13)→C-23 (δ_C 66.0), H_2-26 (δ_C 3.05, 3.34)→C-23 indicated the presence of a hydroxyl group at C-23; 3) H_2-26→C-27 (δ_C 63.8), H_2-26→C-22, H_2-26→C-23 revealed the occurrence of a hydroxyl group at C-27. Next, the configurations at C-22, C-23 and C-25 were discussed. The signal due to the proton adjacent to the hydroxyl group at C-23 appeared at δ 4.04 (dd, J=6.1, 10.4 Hz), therefore C-23-OH oriented in equatorial. The configuration at C-25 was determined to be *S* (axial) by the J values of H_2-26 (1H, d, J=11.0 Hz at δ 3.05; Hax-26; 1H, dd, J=3.4, 11.3 Hz, at δ 3.34, Heq-26). The remaining C-22 configuration was deduced by the comparison of the carbon chemical shift at C-20 of Alkaloids 2, 3, 4 and lycoperosides A, B, D obtained from the aerial[6] or underground[3] parts of tomato. That is, in case of 22α*N*-spirosolane the signal due to C-20 appeared around δ 35.0, while in 22β*N*-isomer it resonated around at δ 43.0, even though oxygen-bearing function substitutes at C-23. In this case, the signal due to C-20 in **3** occerred at δ 35.0, thus indicating its configuration to be 22α*N*(22*S*)-spirosolane. Therefore, the structure of **3** was represented as (5*S*,22*S*,23*S*,25*S*)-3β,23,27-trihydroxy-spirosolane.

Meanwhile, the sugar mixture of the hydrolysate was derived into the corresponding trimethylsilyl ethers of methyl 2-(polyhydroxyalkyl)-thiazolidine-4(*R*)-carboxylates and determined their absolute configurations by GLC. The sugar originating carbon signals deducted sapogenol-originating signals from total signals were assigned to be constituted of one β-D-glucopyranosyl moiety (C-1-6 δ: 104.9, 75.4, 77.6, 71.9, 79.8, 63.0) and one β-lycotetraosyl (β-D-xylopyranosyl-(1→3)-[β-D-glucopyranosyl-(1→2)]-β-D-glucopyranosyl-(1→4)-β-D-galactopyranosyl-) moiety (gal C-1-6 δ: 102.5, 71.9, 74.9, 79.2, 75.1, 60.7, inner glc C-1-6 δ: 105.1, 81.3, 87.0, 70.8, 78.3, 63.0, terminal glc C-1-6 δ: 104.8, 75.3, 78.5, 71.2, 79.2, 62.6, terminal xyl C-1-5 δ: 105.0, 75.6, 76.2, 70.5, 67.3).[8,9] Moreover, HMBC between H_2-26 and C-27-*O*-glucosyl C-1 suggested that the terminal β-D-glucopyranosyl moiety combined to C-27-OH, and the β-lycotetraosyl moiety to C-3-OH. Next, **1** was subjected to enzymatic hydrolysis. With the aid of β-glucosidase (from almond), **1** provided prosapogenin A (**4**), in which carbon signal due to C-27 shifted to δ 63.3 in a higher field, suggesting that the β-D-glucopyranosyl moiety at C-27-OH was eliminated. Therefore, **4** was elucidated as 3-*O*-β-lycotetraosyl esculeogenin A. On the other hand, **1** was treated with tomatinase[10] to afford prosapogenin B (**5**), in which carbon signal at C-3 appeared at δ 70.7 without glycosylation shift, indicating **5**

Table 1. ^{13}C NMR data of esculeosides A (**1**), B (**2**) and their related compounds.

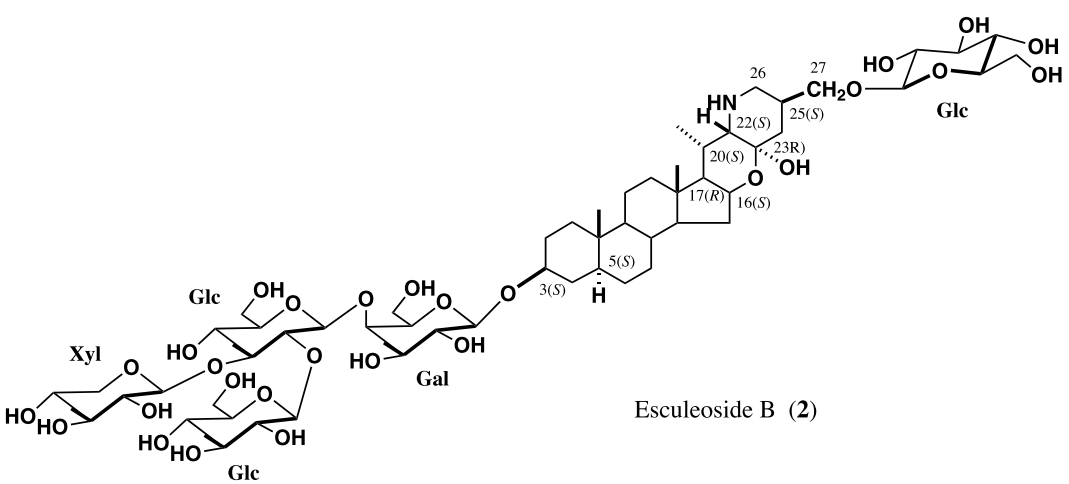
Position	**1**	**3**	**4**	**5**	**2**	**6**
C-1	37.3	37.5	37.3	37.6	37.2	37.2
2	29.9	32.3	29.9	32.3	29.6	29.8
3	77.8	70.6	77.8	70.7	77.6	78.0
4	34.9	39.3	34.9	39.9	34.5	34.8
5	44.8	45.3	44.8	45.3	44.8	44.9
6	29.0	29.1	29.0	29.1	28.7	28.9
7	32.5	32.6	32.5	32.6	32.1	32.2
8	35.4	35.3	35.4	35.4	35.1	35.2
9	54.5	54.7	54.5	54.6	55.0	55.0
10	35.9	35.9	35.9	36.0	35.7	35.8
11	21.2	21.5	21.3	21.4	20.7	20.8
12	40.3	40.8	40.3	40.4	37.2	37.2
13	41.5	41.6	41.5	41.5	42.7	42.8
14	56.3	56.6	56.5	56.6	53.2	53.3
15	32.3	32.5	32.3	32.5	33.4	33.7
16	78.7	79.6	78.7	79.2	69.4	69.2
17	62.8	63.0	62.8	62.9	57.7	57.9
18	16.5	17.0	16.5	16.5	14.8	15.0
19	12.3	12.5	12.3	12.6	12.3	12.3
20	35.4	35.0	35.4	35.5	26.4	26.7
21	15.0	15.2	15.0	15.0	19.0	19.6
22	99.1	101.7	99.2	99.1	59.5	59.8
23	68.4	66.0	68.5	68.4	93.4	93.5
24	29.1	33.7	29.5	29.1	39.4	40.0
25	35.6	38.1	38.1	35.6	32.9	35.4
26	39.9	40.3	40.3	39.9	47.9	48.2
27	70.8	63.8	63.3	70.8	71.3	63.5
OAc	21.2		21.2	21.2		
	170.7		170.7	170.7		
gal C-1	102.5		102.5		102.2	102.4
2	71.9		73.2		72.6	72.8
3	74.9		75.4		75.0	75.2
4	79.2		79.9		79.7	79.6
5	75.1		75.6		74.6	74.8
6	60.7		60.7		60.9	60.7
Inner glc C-1	105.1		105.1		104.1	104.5
2	81.3		81.3		80.3	80.8
3	87.0		87.0		87.0	87.0
4	70.8		70.8		70.3	70.1
5	78.3		77.6		77.3	77.2
6	63.0		63.0		62.3	62.2
Terminal glc C-1	104.8		105.0		104.3	104.6
2	75.3		76.2		75.3	75.7
3	78.5		79.2		78.0	78.0
4	71.2		70.5		71.0	71.0
5	79.2		77.8		78.4	78.2
6	62.6		62.6		62.0	62.6
Terminal xyl C-1	105.0		104.8		103.8	104.3
2	75.6		75.1		74.4	75.2
3	76.2		77.6		77.5	77.5
4	70.5		71.2		69.7	70.5
5	67.3		67.3		66.6	67.0
27-O glc C-1	104.9			105.0	103.7	
2	75.4			75.4	75.0	
3	77.6			78.4	77.7	
4	71.9			71.9	71.2	
5	79.8			78.6	77.6	
6	63.0			63.0	62.3	



Esculeoside A (**1**)

to be 27-*O*-β-D-glucopyranosyl esculeogenin A. Furthermore, in the ^{1}H NMR spectrum of **1**, one acetyl group appeared at δ 2.11 and it attached to C-23-OH by the HMBC between H-23 and acetyl carbonyl group. A methine proton signal at C-23 displayed at δ 5.38 (1H, dd, J=5.5, 11.0 Hz), which indicated α-configuration of the acetoxyl group. Consequently, the structure of **1** was determined as 3-*O*-β-lycotetraosyl (5*S*,22*S*,23*S*,25*S*)-23-acetoxy-3β,27-dihydroxyspirosolane 27-*O*-β-D-glucopyranoside.

On the other hand, from the red color-type tomato, a major steroidal alkaloid glycoside, esculeoside B (**2**) has been obtained. After the cultivated red color-type tomato (6.5 kg) called as Italian San Marzano was smashed in water, the sediment was removed by centrifugation and the supernatant was passed through Diaion HP-20 eluting with water and MeOH, successively. The methanolic eluate was concentrated to give a syrup, which was then subjected to reversed silica gel column chromatography eluted with 40% aq.MeOH and 60% aq.MeOH, successively. The latter eluate provided esculeoside B (**2**, 1210 mg) as an an amorphous powder showing $[\alpha]_D$ −49.2° (pyridine). The HR-FABMS of **2** showed a peak at *m*/*z* 1228.5964 corresponding to a molecular formula $[C_{56}H_{93}NO_{28}+H]^+$ (Calcd for 1228.5962). Acid hydrolysis gave inseparable complicated sapogenols being different from the case of **1**. The ^{1}H NMR spectrum (in pyridine-d_5) showed two tertiary methyl signals at δ 0.75 and 0.92, one secondary methyl signal at δ 1.62 (d, J=7.5 Hz) together with five anomeric proton signals at δ 4.79 (d, J=7.5Hz), 4.91 (d, J=7.3 Hz), 5.09 (d, J=7.3 Hz), 5.11 (d, J=7.3 Hz) and 5.48 (d, J=7.5 Hz). Besides ^{13}C NMR signals (in pyridine-d_5, Table 1) due to a β-lycotetraosyl moiety[8,9] and the β-D-glucopyranosyl moiety as well as in case of **1**, total 27 carbon signals comprised of three methyls (δ 12.3, 14.8, 19.0), one hydroxymethyl (δ 71.3), one hemiketal carbon (δ 93.4), one nitrogen-bearing methine carbon (δ 59.5), one nitrogen-bearing methylene carbon (δ 47.9) and two oxygen-bearing methine carbons (δ 69.4, 77.6). By the aid of FG-COSY, HMQC and HMBC, all of the carbon signals of **2** were assigned as follows (Table 1): C-1-27 of sapogenol moiety: δ 37.2, 29.6, 77.6, 34.5, 44.8, 28.7, 32.1, 35.1, 55.0, 35.7, 20.7, 37.2, 42.7, 53.2, 33.4, 69.4, 57.7, 14.8, 12.3, 26.4, 19.0, 59.5, 93.4, 39.4, 32.9, 47.9, 71.3. 3-*O*-β-lycotetraosyl moiety, gal C-1-6: 102.2, 72.6, 75.0, 79.7, 74.6, 60.9, inner glc C-1-6: 104.1, 80.3, 87.0, 70.3, 77.3, 62.3, terminal glc C-1-6: 104.3, 75.3, 78.0, 71.0, 78.4, 62.0, terminal xyl C-1-5: 103.8, 74.4, 77.5, 69.7, 66.6, 27-*O*-glc C-1-6: 103.7, 75.0, 77.7, 71.2, 77.6, 62.3. On this assignment, especially, the HMBC between H_3-21 and C-20, C-22 as illustrated in Figure 2, and the occurrence of the hemiketal carbon function conclusively characterized a novel sapogenol moiety, which has a rare natural product, solanocapsine-type framework.[11–14] Next, NOESY led to the assignments of the configurations at C-22 and C-23. Namely, the observation of NOESY between H-20 and H-22, and between H-26 and H-22 revealed the configurations of both H-20 and H-22 to be *cis*-correlation. The



Esculeoside B (**2**)

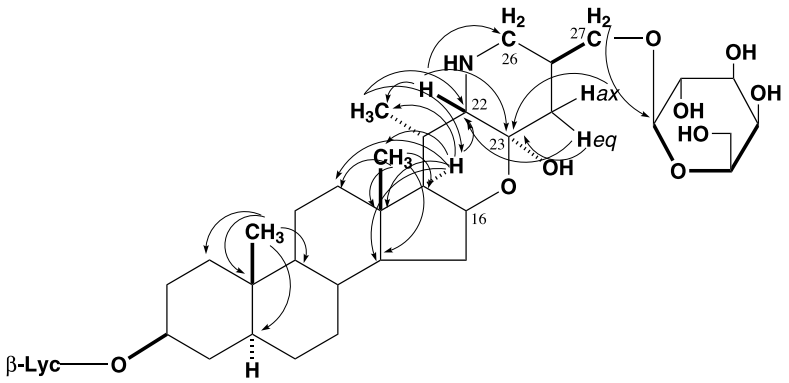


Figure 2. Key HMBC of esculeoside B (**2**).

configuration at C-25 was also deduced to be *S* since the Hax-26 signal appeared at δ 3.44 (t-like, J=12.5 Hz). The configuration of the hydroxyl group at C-23 was estimated as α-axial by the reason that H_3-21 signals shifted toward lower field at δ 1.62 in a 1,3-diaxial correlation with C-23-OH group. Enzymatic hydrolysis of **2** with β-glucosidase provided a 3-*O*-β-lycotetraoside, prosapogenin C (**6**). Moreover, the HMBC between C-27 and galactopyranosyl H-1 indicated the presence of the sugar linkages, 3-*O*-β-lycotetraosyl and 27-*O*-β-D-glucopyranosyl moieties.

Consequently, the structure of **2** could be represented as 3-*O*-β-lycotetraosyl (5*S*,22*S*,23*R*,25*S*)-22,26-epimino-16β,23-epoxy-3β,23,27-trihydroxycholestane 27-*O*-β-D-glucopyranoside.

3. Biological evaluation

Taking into account the fact that the steroidal alkaloid glycosides possess cytotoxic activity against various tumour cell lines,[15,16] these tomato steroidal alkaloid glycosides, esculeosides A (**1**) and B (**2**), could be also expected to possess potent anti-cancer activity. Growth inhibition of esculeoside A (**1**) against MCF7 (human breast cancer cell) and B16F2F (mouse melanoma cell) cells has been evaluated. Cytotoxicities for these compounds were measured using the WST-8 assay method.[17] The GI_{50} values of **1** were 13.3 and 7.9 μM against MCF7 and B16F2F, respectively. Anti-herpes (anti-HSV-1) activity[18] of esculeogenin A (**3**) was also evaluated.[19] It showed EC_{50} 42 μg/ml.

4. Conclusion

It is worthy of note that novel steroidal alkaloid glycosides, esculeoside A (**1**) having spirosolane skeleton in a yield of 0.025 and 0.004% from the Cherry tomato and the pink color-type tomato (Momotaro), respectively, and esculeoside B (**2**) having solanocapsine skeleton in a yield of 0.019% from the red color-type tomato have been isolated for the first time. Esculeosides A (**1**) and B (**2**) might be produced from tomatine in the immature tomato as tomato grows mature, and plausible chemical correlation between **1** and **2** was assumed as shown in Chart 1. The hydroxy group at C-23 would turn to an enol by E-ring fission, followed by ring closure of the C-16-oxygen anion to the C-23 carbonium center to afford esculeoside B (**2**).

The isolation of the steroidal alkaloid glycosides having anti-cancer activity from tomato fruits has firstly been attained, and the intake of tomato is regarded to be effective for reducing the risk of cancer in cooperation with the

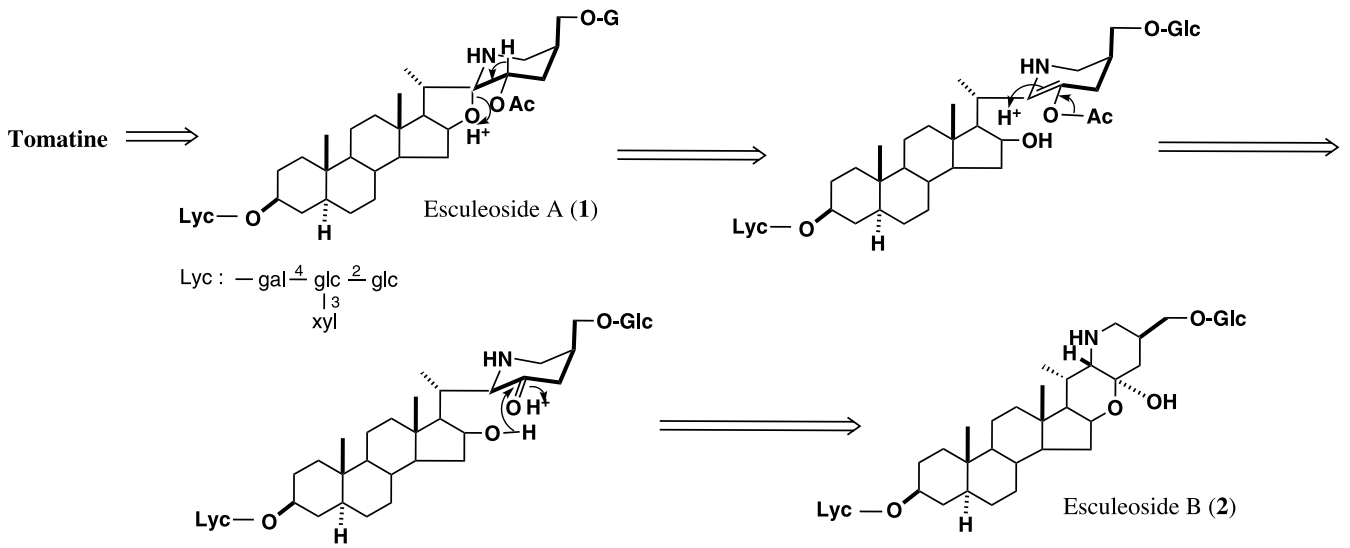


Chart 1. Plausible chemical correlation between esculeoside A (**1**) and B (**2**).

occurrence of lycopene. Investigation of other biological function is now in progress.

5. Experimental

5.1. General procedures

Mps: uncorr.; Optical rotations were measured with a JASCO DIP-1000 KUY polarimeter (l=0.5); NMR spectra were measured in pyridine-d_5 on a JEOL α-500 spectrometer and chemical shifts were referenced to TMS; FABMS were obtained with a glycerol matrix in the positive ion mode using a JEOL JMS-DX-303HF spectrometer; GLC was performed on an HP5890A gas chromatograph with a flame ionization detector (FID); Column chromatography was carried out with silica gel 60 (Art. 7734 and Art. 9385, Merck), Diaion HP-20P (Mitsubishi Chemical Industries Co., Ltd) and Chromatorex ODS (Fuji Silysia Chemical Co., Ltd), and TLC was performed on a precoated silica gel 60 F_{254} (Merck) and RP-18 $F_{254}S$ (Merck). Fetal calf (FCS) was purchased from Gibro BRL. Sulfonated γ-globulin (Venilon) was supplied by the Chemo-Sero Therapeutic Institute.

5.2. Extraction and isolation of esculeoside A (1)

The fresh ripe fruits (1.78 kg) of Cherry tomato (*Lycopersicon esculentum* var. *cerasiforme*) purchased in Kumamoto city were smashed, added with water and centrifused. The supernatant was passed through Diaion HP-20 and eluted with water and MeOH, successively. The MeOH eluate was then subjected to ODS eluted with starting from 40% aq. MeOH to MeOH, gradiently. The 70% eluate provided esculeoside A (**1**, 440 mg). Similarly, from the pink type tomato [*L. esculentum* (Momotaro)] (7.53 kg), esculeoside A (**1**) was obtained in a yield of 311 mg.

5.2.1. Esculeoside A (1). Colorless needles, mp 225 °C (decomp.); $[\alpha]_D^{26}$ −52.5° (*c*0.60, MeOH); positive HR-FABMS (*m/z*): 1292.5869 $[M+Na]^+$ ($C_{58}H_{95}NO_{29}Na$, Calcd for 1292.5883); ^{1}H NMR (pyridine-d_5) δ: 0.66 (3H, s, H_3-19), 0.89 (3H, s, H_3-18), 1.07 (3H, d, J=6.7 Hz, H_3-21), 2.11 (3H, s, acetyl), 4.88 (1H, d, J=7.3 Hz), 4.89 (1H, d, J=7.9 Hz), 5.19 (1H, d, J=7.9 Hz), 5.23 (1H, d, J=7.9 Hz), 5.38 (1H, dd, J=5.5, 11.0 Hz, H-23), 5.57 (1H, d, J=7.3 Hz).

5.2.2. Esculeogenin A (3). After esculeoside A (**1**, 126 mg) was hydrolyzed with 2 N HCl, the reaction mixture was extracted with AcOEt. The organic layer was evaporated in vacuo to afford a residue which was purified by silica gel column chromatography with $CHCl_3$–MeOH–water=9:1:0.1 to give esculeogenin A (**3**, 14 mg). Colorless needles, mp 215–220 °C, $[\alpha]_D^{26}$ −99.6° (*c* 0.70, pyridine); EI-MS (*m/z*): 447 [M, $C_{27}H_{45}NO_4$](base peak), 170 $[C_9H_{18}NO_2]^+$(30%), 146 $[C_6H_{12}NO_3]^+$ (13%); ^{1}H NMR (pyridine-d_5) δ: 0.78 (3H, s, H_3-19), 1.01 (3H, s, H_3-18), 1.08 (3H, d, J=6.7 Hz, H_3-21), 3.01 (1H, t-like, J=7.3 Hz, H-20), 3.05 (1H, d, J=11.0 Hz, Hax-26), 3.34 (1H, dd, J=3.4, 11.0 Hz, Heq-26), 3.82 (1H, m, H-3), 4.04 (2H, dd, J=6.1, 10.4 Hz, H-23, 27a), 4.22 (1H, dd, J=7.9, 10.4 Hz, H-27b), 4.49 (1H, dd, J=7.3, 15.9 Hz, H-16).

5.2.3. Analysis of sugar components of 1 and 2. The above hydrolyzed aqueous portion was passed through Amberlite IRA400 and the eluate was concentrated to dryness in vacuo to give a residue, which was dissolved in dry pyridine, then L-cysteine methyl ester hydrochloride was added to the solution. The reaction mixture was heated at 60 °C for 2 h and concentrated to dryness using N_2. To the residue was added trimethylsilylimidazole, and the mixture was heated at 60 °C for 1 h. The reaction mixture was concentrated to dryness, and The residue was extracted with a mixture of hexane and H_2O, and the organic layer was analyzed by gas liquid chromatography (GLC); column: OV-17 (0.32 mm×30 m), detector: FID, column temp.: 230 °C, injector temp.: 270 °C, carrier gas: He (2.2 kg/cm^2). Each peak was observed at t_R (min); 17′16″ (D-glc), 16′54″ (D-gal), 11′71″ (L-rha) 9′82″ (D-xyl). The standard monosaccharides were subjected to the same reaction and GLC analysis under the same condition.

5.2.4. Prosapogenin A (4). A mixture of esculeoside A (**1**, 30 mg) and β-glucosidase (from almond, 10 mg) in acetic acid-sodium acetate buffer (10 ml) was incubated at 37 °C for 1 day. After filtration, the filtrate was passed through Diaion HP-20 with water, and then recovered with MeOH to afford the residue, which was purified on silica gel column chromatography with $CHCl_3$–MeOH–water=8:2:0.2→6:4:1 to provide prosapogenin A (**4**, 10 mg). An amorphous powder, ^{1}H NMR (pyridine-d_5) δ: 0.68 (3H, s, H_3-19), 0.91 (3H, s, H_3-18), 1.08 (3H, d, J=7.6 Hz, H_3-21), 2.14 (3H, s, acetyl), 3.05 (1H, d, J=11.6 Hz, Hax-26), 3.33 (1H, dd, J=3.4, 11.0 Hz, Heq-26), 4.84 (1H, d, J=7.3 Hz), 5.14 (1H, d, J=7.9 Hz), 5.19 (1H, d, J=7.3 Hz), 5.44 (1H, dd, J=5.2, 11.9 Hz, H-23), 5.53 (1H, d, J=7.9 Hz).

5.2.5. Prosapogenin B (5). A mixture of esculeoside A (**1**, 50 mg) and tomatinase[10] (3 ml) in citric acid buffer (3 ml) was left stand at r. t. for one day. After filtration, the filtrate was passed through Diaion HP-20 column with water and subsequently MeOH. The MeOH eluate was subjected to silica gel column chromatography with $CHCl_3$–MeOH–water=9:1:0.1→7:3:0.5 to give prosapogenin B (**5**, 8 mg). An amorphous powder, ^{1}H NMR (pyridine-d_5) δ: 0.83 (3H, s, H_3-19), 0.92 (3H, s, H_3-18), 1.08 (3H, d, J=7.6 Hz, H_3-21), 2.12(3H, s, acetyl), 2.87 (1H, d, J=9.8 Hz, Hax-26), 3.25 (1H, br d, J=8.5 Hz, Heq-26), 4.90 (1H, d, J=7.9 Hz), 5.40 (1H, dd, J=5.2, 11.3 Hz, H-23).

5.3. Extraction and isolation of esculeoside B (2)

The fresh ripe fruits (6.5 kg) of Italian San Marzano (*Lycopersicon esculentum*) cultivated at Kumamoto city were smashed, added with water and centrifused. The supernatant was passed through Diaion HP-20 and eluted with water and MeOH, successively. The MeOH eluate was then subjected to ODS eluted with starting from 40% aq. MeOH to MeOH, gradiently. The 70% eluate provided esculeoside B (**2**, 1210 mg).

5.3.1. Esculeoside B (2). An amorphous powder, $[\alpha]_D^{26}$ −49.2° (*c* 0.60, pyridine); positive HRFAB-MS (*m/z*): 1228.5964 $[C_{56}H_{93}NO_{28}+H]^+$; ^{1}H NMR (pyridine-$d_5$) δ: 0.75 (3H, s, H_3-19), 0.92 (3H, s, H_3-18), 1.62 (3H, d,

J=7.5 Hz, H_3-21), 2.61 (1H, dq-like, J=6.5, 7.5 Hz, H-20), 3.57 (1H, J=6.5 Hz, H-22), 3.44, 4.10 (2H, t-like, J=12.5 Hz, H_2-26), 4.79 (1H, d, J=7.5 Hz), 4.91 (1H, d, J=7.3 Hz), 5.09 (1H, d, J=7.3 Hz), 5.11 (1H, d, J=7.3 Hz), 5.48 (1H, d, J=7.5 Hz).

5.3.2. Prosapogenin C (6). A mixture of esculeoside B (**2**, 30 mg) and β-glucosidase (from Almond, 10 mg) in acetic acid-sodium acetate buffer (10 ml) was incubated at 37 °C for 1 day. After filtration, the filtrate was passed through Diaion HP-20 with water, and then recovered with MeOH to afford the residue, which was purified on silica gel column chromatography with $CHCl_3$–MeOH–water=8:2:0.2→6:4:1 to provide prosapogenin C (**6**, 10 mg). An amorphous powder, ^{1}H NMR (pyridine-d_5) δ: 0.65 (3H, s, H_3-19), 1.02 (3H, s, H_3-18), 1.71 (3H, d, J=7.6 Hz, H_3-21), 3.52 (1H, t-like, J=12.5 Hz, Hax-26), 4.10 (1H, overlap, Heq-26), 4.93 (1H, d, J=7.3 Hz), 5.15 (1H, d, J=7.9 Hz), 5.18 (1H, d, J=7.9 Hz), 5.57 (1H, d, J=7.9 Hz).

5.4. Cytotoxic and anti-HSV-1 activities

MCF7 cells were supplied by the Cell Resource Center for the Biomedical Research, Institute of Development, Aging and Cancer, Tohoku University. B16F2F cells were supplied by the Riken Bioresource Center. Both cell lines were maintained in RPMI1640 medium with 10% FBS at 37 °C under 5% CO_2 atmosphere. Cytotoxic experiments were carried out in quadruplicate in 96-well microplates, and the amount of viable cells at the end of the incubation was determined by using an WST-8 assay.[17] GI_{50} values of CDDP were 2.28 and 13.0 μM againt MCF7 and B16F2F, respectively. HSV-1 strain KOS and Vero cells were provided by the Chemo-Sero Therapeutic Institute. The antiviral activity of test samples on HSV-1 (KOS) was measured by the plaque assay[19] described previous paper.[18] EC_{50} of acyclovir was 0.39 μg/ml.

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Total syntheses of the strobilurins G, M, and N

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Dedicated to Professor Heidrun Anke on the occasion of her 60th birthday

Abstract—The key reactions in the general synthesis of strobilurins are the highly (*Z*)-selective Wittig reaction of an (*E*)-cinnamaldehyde with the phosphorus ylide **8** derived from (1,1-dibromoethyl)triphenylphosphonium bromide, followed by bromine–iodine exchange and Pd–Cu co-catalyzed Stille cross-coupling of the resulting alkenyl iodide with methyl (*Z*)-2-tributylstannyl-3-methoxyacrylate (**7**). The synthetic strobilurins G, M, and N were identical with the corresponding natural compounds. In addition, the (2′ *S*)-configuration of strobilurin G (**1**) was unambiguously established by oxidative degradation of the synthetic intermediate (*S*)-**9** to (*R*)-2,3-dihydroxyisovaleric acid.

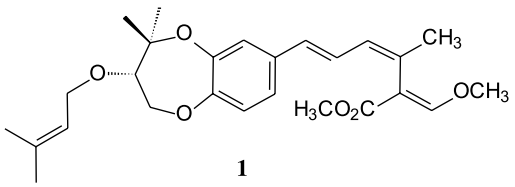
1. Introduction

Strobilurins[1] are important antifungal antibiotics which have served as lead compounds for the development of a new generation of industrial fungicides for crop protection.[2] More complex compounds of this group include strobilurin G (=strobilurin D) (**1**), M (**2**), and N (**3**), which contain 1,4-dioxepin or 1,4-dioxin moieties attached to the phenyl ring. Strobilurin G is produced by cultures of several basidiomycetes[3] and the ascomycete *Camarops* (*Bolinia*) *lutea*,[4] strobilurin M by an unidentified tropical *Mycena* species,[5] and the biologically inactive strobilurin N by fruit bodies of *Mycena crocata*.[6]

Known methods for the synthesis of strobilurins involve multistep procedures in which the (*Z*)-β-methoxyacrylate toxophore is formed by the addition of a C-1 reagent to an ester or keto ester in the last step.[7] Herein, total syntheses of the title compounds based on a novel strategy are presented. Retrosynthetic analysis indicated that the strobilurin side chain could be formed by stereoselective coupling of an appropriate (*Z*)-dienyl halide **5** with methyl (*Z*)-2-tributylstannyl-3-methoxypropenoate (**7**) (Scheme 1). The latter has been introduced by Hodgson et al.[8] for the synthesis of simple strobilurin analogues by Pd/Cu co-catalyzed cross-coupling with aryl iodides. Formation of the dienyl halides **5** (X=Br) should be realised with high (*Z*)-stereoselectivity via the Wittig reaction of an appropriate cinnamaldehyde **6** with the phosphorus ylide **8** derived from (1,1-dibromoethyl)triphenylphosphonium bromide.[9]

2. Results and discussion

To apply this strategy for the synthesis of strobilurin G (**1**), the optically active cinnamaldehyde **13** was needed as the



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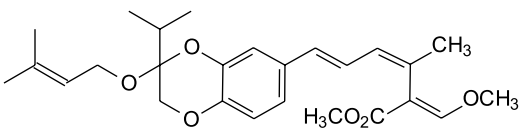

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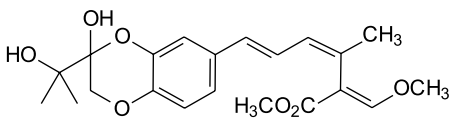

3

Keywords: Strobilurins; Benzodioxepins; Fungicides; Natural products; Total synthesis.
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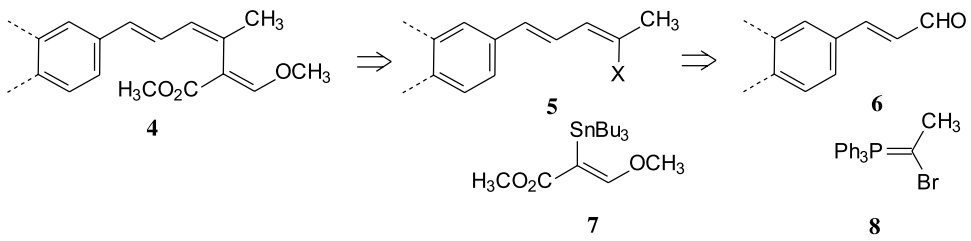


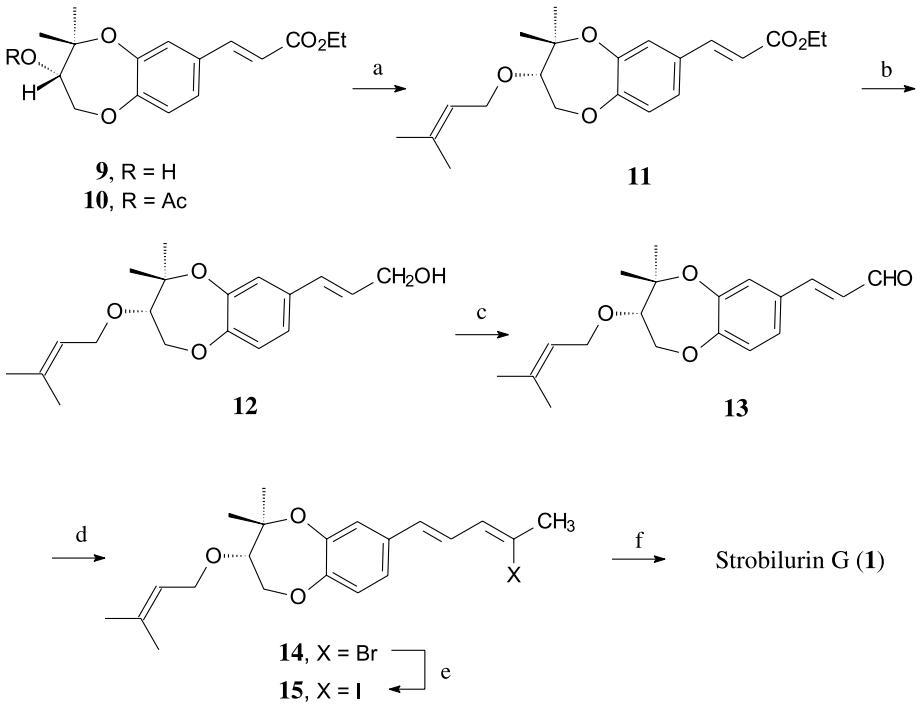
Scheme 1. Retrosynthetic analysis for the strobilurin side chain.

starting material (Scheme 2). Compound **13** was obtained in three steps from the known alcohol **9** (78% ee), a relay substance used previously in structural investigations of strobilurin G and related antibiotics.[3a] Alkylation of **9** with 3,3-dimethylallyl bromide afforded ester **11**, which after reduction with DIBAL-H and oxidation of the resulting allylic alcohol **12** with MnO_2 yielded aldehyde **13**. Reaction of the latter with the phosphorus ylide **8** generated from (1,1-dibromoethyl)triphenylphosphonium bromide via halogen–metal exchange[9] afforded a 5:1 mixture of the (*E*,*Z*)- and (*E*,*E*)-isomers of dienyl bromide **14**. The isomers, identified by their NMR spectra and NOE experiments, were easily separated by column chromatography. The desired (*E*,*Z*)-diene **14** was thereby obtained in 40% yield.

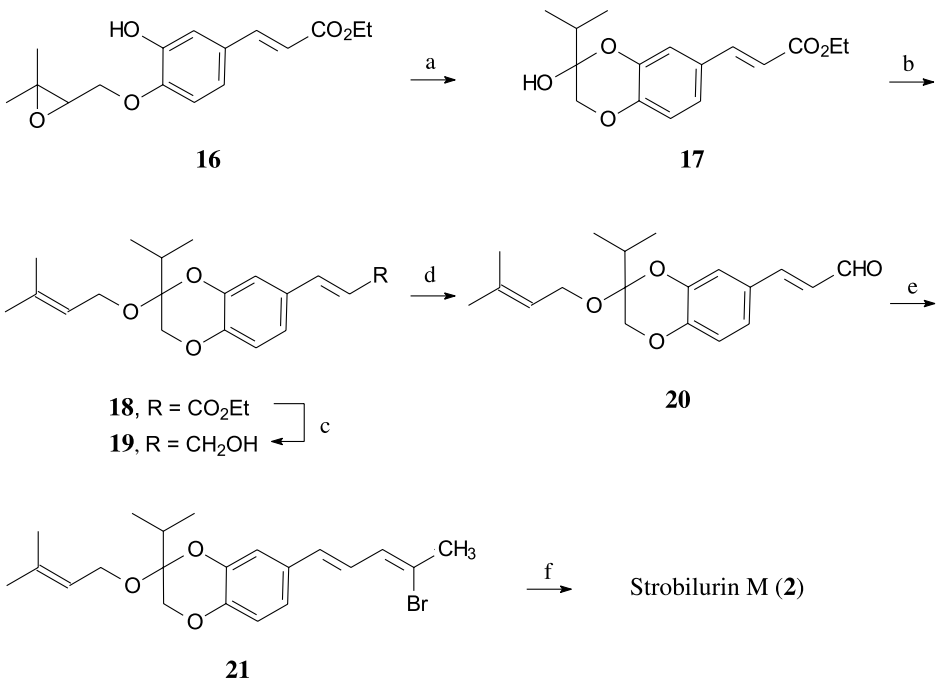
The bromide **14** was inert to Stille coupling with stannyl reagent **7** and therefore had to be converted into the more reactive iodide **15** by copper(I)-mediated halogen exchange.[10,11] Treatment of **14** with *n*-butyl lithium and molecular iodine in succession afforded significantly lower yields. Pd/Cu co-catalyzed cross-coupling[8] of iodide **15** with methyl (*Z*)-2-tributylstannyl-3-methoxypropenoate (**7**) under mild conditions gave **1** in 38% yield. The low yield reflects the instability of the iodide, which decomposes within a few days, even at 4 °C. Experiments to introduce the methoxyacrylate residue via Rossi's zinc reagent[12] were unsuccessful. A comparison of the spectroscopic data and optical rotations of synthetic and natural strobilurin G[4] proved their identity. The optical rotation of the synthetic product, $[\alpha]_D^{20}=+20.3$, relates to 79% ee, which corresponds to that of alcohol **9** used for the synthesis.

The stereochemistry of alcohol **9** had been previously determined as (2′*S*) by application of the high field NMR variant of Mosher's method.[3a] In order to prove this assignment, the acetate **10** derived from **9**, was subjected to a ruthenium-mediated oxidative degradation following a procedure of Bringmann et al.[13] The optical rotation of the resulting (*R*)-2,3-dihydroxyisovaleric acid, $[\alpha]_D^{20}=9.5$ (*c* 0.2, 0.1 N HCl), agrees well with that of the literature, $[\alpha]_D^{20}=12.1$ (*c* 0.1, 0.1 N HCl),[14] taking into account the optical purity of the starting material. Since alcohol **9** had been correlated to strobilurin G as well as to strobilurins I and K before,[3a] the (2′*S*)-configuration can now be safely assigned to all three compounds.

In contrast to strobilurin G (**1**), the isomeric strobilurin M (**2**) occurs in racemic form.[5] The benzodioxin moiety



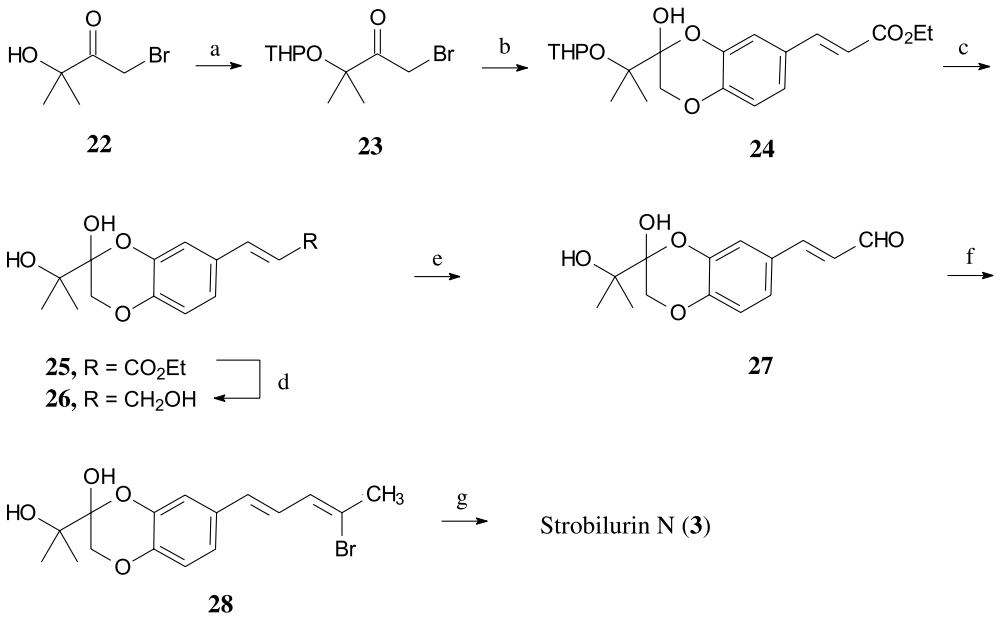
Scheme 2. Synthesis of strobilurin G (**1**). Reagents and conditions: (a) 3,3-dimethylallyl bromide, NaH, DMF, 0 °C, 68%. (b) DIBAL-H, THF, −78 °C, 92%. (c) MnO_2, CH_2Cl_2, 87%. (d) **8**, THF, −50 °C, 2 h, 40%. (e) KI, CuI, HMPT, 120 °C, 2 d, 63%. (f) **7**, CuI, $Pd(PPh_3)_4$, NMP, 50 °C, 24 h, 38%. Yields correspond to chromatographically pure compounds.



Scheme 3. Synthesis of strobilurin M (**2**). Reagents and conditions: (a) $SnCl_4$, THF, 2 h, 44%. (b) 3,3-dimethylallyl bromide, NaH, DMF, 0 °C, 32%. (c) DIBAL-H, THF, −78 °C, 92%. (d) MnO_2, CH_2Cl_2, 69%. (e) **8**, THF, −50 °C, 2 h, 47%. (f) 1. KI, CuI, HMPT, 120 °C, 2 d; 2. **7**, CuI, $Pd(PPh_3)_4$, NMP, 50 °C, 24 h, 19%. Yields relate to chromatographically pure compounds.

present in **2** could be prepared in 44% yield via $SnCl_4$[15] catalysed cyclisation of the epoxide **16** in THF (Scheme 3). The resulting hemiacetal **17** was alkylated with 3,3-dimethylallyl bromide to yield acetal **18**. Experiments to obtain this compound via acid-catalyzed acetalisation were unsuccessful. The ester **18** was converted into the dienyl bromide **21** by the same reaction sequence as described above. Due to the instability of the corresponding iodide, the latter was directly used for the Stille coupling with **7** to give strobilurin M (**2**) in low yield. The spectroscopic data of **2** were identical with those of the natural product,[5] confirming the proposed structure.

The synthesis of strobilurin N (**3**) commences from ester **24** (Scheme 4), prepared in 29% yield by condensation of ethyl 3,4-dihydroxycinnamate with the bromoketone **23**.[7d,16] A similar 1.4-benzodioxin ring formation had been used in our synthesis of strobilurin E.[7d] Small amounts of a disubstitution product were removed by chromatography on silica gel. Reaction of **24** with a catalytic amount of pyridinium



Scheme 4. Synthesis of strobilurin N. Reagents and conditions: (a) dihydropyran, PPTS, 20 °C, 4 h, 91%. (b) Ethyl 3,4-dihydroxycinnamate, K_2CO_3, acetone, 80 °C, 3 h, 29%. (c) PPTS (cat.), EtOH, 90 °C, 2 h, 48%. (d) DIBAL-H, THF, −78 °C, 20%. (e) MnO_2, CH_2Cl_2, 28%. (f) **8**, THF, −50 °C, 2 h, 38%. (g) 1. KI, CuI, HMPT, 120 °C, 2 d; 2. **7**, CuI, $Pd(PPh_3)_4$, NMP, 50 °C, 24 h, 23%. PPTS, pyridinium *p*-toluenesulfonate. NMP, 1-methyl-2-pyrrolidinone. Yields relate to chromatographically pure compounds.

p-toluene sulfonate (PPTS)[17] in ethanol cleaved the protecting group and afforded diol **25** in 48% yield. The latter was converted to the (*Z*)-vinyl bromide **28** by the reaction sequence used in the synthesis of strobilurin G and M. The iodine derivative corresponding to **28** was again unstable and had to be used without further purification for the final coupling. The resulting strobilurin N (**3**) was identical with the natural product.[6]

3. Conclusions

In conclusion, a simple procedure for assembling the strobilurin side chain from (*E*)-cinnamaldehydes has been developed, in which α-bromoethylidene ylide **8** and (*Z*)-2-tributylstannyl-3-methoxypropenoate (**7**) serve as building blocks. The Pd–Cu-catalyzed coupling between the (*E*,*Z*)-dienyl iodides **5** and stannyl reagent **7** needs further optimization. Furthermore, the direct synthesis of iodides **5** from the corresponding α-iodoethylidene ylide[11] can be considered.

4. Experimental

4.1. General

Melting points (uncorrected): Reichert Thermovar; Optical rotations: Perkin–Elmer 214; UV/Vis and CD: Instruments S. A. Jobin Yvon CD-6-Dichrograph; IR: Bruker FTIR spectrophotometer IFS 45; NMR: Bruker AMX 600 and ARX 300 with solvent peak as internal reference ($CDCl_3$: δ_H 7.24, δ_C 77.0; CD_3OD: δ_H 3.35, δ_C 49.0; [D_6]acetone: δ_H 2.04, δ_C 29.8). Long range $^1H-^{13}C$ connectivities were determined by inverse experiments using gradient pulses optimised for a coupling constant of ~7 Hz; TLC: silica gel Merck G plates; column chromatography: silica gel Merck 60; MS (EI) and HRMS (EI) were performed on a Finnigan MAT 95 double focusing mass spectrometer, equipped with an EI ion source operated at 70 eV.

4.2. Synthesis of strobilurin G

4.2.1. Ethyl (*S*)-3-{4,4-dimethyl-3-(3-methylbut-2-enyloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl}acrylate (11). To a suspension of NaH (76.0 mg, 3.15 mmol) in DMF (10 mL) were added at 0 °C a solution of **9**[3a] (0.62 g, 2.10 mmol, 78% ee) in DMF (10 mL) and 3,3-dimethylallyl bromide (0.38 mL, 3.15 mmol). After 16 h, 2 N HCl (10 mL) was added and the reaction mixture extracted with EtOAc (3×). The organic layers were washed with water (2×) and dried ($MgSO_4$). Evaporation and purification of the residue by column chromatography (hexanes–EtOAc, 3:1, v/v) yielded **11** (0.70 g, 92%) as an orange oil, $[\alpha]_D^{20}$=+26.6 (*c* 1, $CDCl_3$); R_f=0.76 (hexanes–EtOAc, 3:1, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ=1.25 (s, 3H), 1.32 (t, *J*=7.2 Hz, 3H), 1.40 (s, 3H), 1.68 (d, *J*=1.3 Hz, 3H), 1.75 (d, *J*=1.3 Hz, 3H), 3.57 (dd, *J*=11.0, 6.6 Hz, 1H), 3.67 (dd, *J*=11.0, 3.8 Hz, 1H), 4.03 (dd, *J*=6.6, 3.8 Hz, 1H), 4.05 (d, *J*=7.0 Hz, 2H), 5.36 (tqq, *J*=7.0, 1.3, 1.3 Hz, 1H), 6.26 (d, *J*=15.9 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 1H), 7.01 (d, *J*=2.0 Hz, 1H), 7.02 (dd, *J*=8.8, 2.0 Hz, 1H), 7.56 (d, *J*=15.9 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.4, 18.1, 20.6, 25.0, 25.9, 60.4, 68.0, 68.9, 74.2, 79.7, 116.3, 116.7, 117.4, 120.7, 121.7, 128.4, 137.7, 142.4, 144.4, 144.5, 167.3; MS (EI): *m*/*z* (rel. int.) 360 (100) [M^+], 293 (16), 292 (15), 248 (19), 234 (12), 233 (27), 208 (35), 163 (10), 69 (38), 40 (28); HRMS (EI) calcd for $C_{21}H_{28}O_5$ 360.1937, found 360.1947; Anal. calcd C, 69.98; H, 7.83; found C, 69.81; H, 8.12.

4.2.2. (*S*)-3-{4,4-Dimethyl-3-(3-methylbut-2-enyloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]-dioxepin-7-yl}-2-propen-1-ol (12). To a solution of **11** (0.29 g, 0.91 mmol) in THF (20 mL) was added dropwise a solution of DIBAL-H (1.5 M in THF, 3.50 mL, 5.25 mmol) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C, then carefully quenched with water (1 mL) and warmed to rt. After dilution with EtOAc (20.0 mL), the solution was washed with 2 N HCl (3×) and water and dried over $MgSO_4$. Concentration and column chromatography of the residue (hexanes–EtOAc, 1:1, v/v) furnished **12** (0.29 g, 87%, 78% ee) as an orange oil, $[\alpha]_D^{20}$=+26.0 (*c* 1, MeOH); R_f=0.66 (hexanes–EtOAc, 1:1); ^1H NMR (300 MHz, [D_6]acetone) δ 1.21 (s, 3H), 1.38 (s, 3H), 1.66 (s, *J*=1.4 Hz, 3H), 1.72 (s, *J*=1.4 Hz, 3H), 2.81 (br, 1H, OH), 3.56 (dd, *J*=10.9, 6.2 Hz, 1H), 3.70 (dd, *J*=10.9, 3.9 Hz, 1H), 3.95 (dd, *J*=6.2, 3.9 Hz, 1H), 4.04 (d, *J*=6.7 Hz, 2H), 4.18 (dd, *J*=5.4, 1.4 Hz, 2H), 5.49 (tqq, *J*=6.7, 1.4, 1.4 Hz, 1H), 6.22 (dt, *J*=15.9, 5.4 Hz, 1H), 6.47 (dt, *J*=15.9, 1.4 Hz, 1H), 6.79 (d, *J*=8.3 Hz, 1H), 6.85 (d, *J*=2.0 Hz, 1H), 6.87 (dd, *J*=8.2, 2.0 Hz, 1H); ^{13}C NMR (75.6 MHz, [D_6]acetone) δ 18.0, 20.7, 25.1, 25.8, 63.3, 68.2, 69.6, 74.9, 80.3, 115.5, 117.4, 120.0, 122.3, 129.2, 129.7, 132.2, 136.9, 142.9, 143.2; MS (EI): *m*/*z* (rel. int.) 318 (100) [M^+], 191 (17), 166 (13), 69 (33), 41 (16); HRMS (EI) calcd for $C_{19}H_{26}O_4$ 318.1831, found 318.1825; Anal. calcd C, 71.67; H, 8.23; found C, 71.60; H, 8.63.

4.2.3. (*S*)-3-{4,4-Dimethyl-3-(3-methylbut-2-enyloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]-dioxepin-7-yl}propenal (13). To a suspension of MnO_2 (2.00 g, 23.0 mmol) in CH_2Cl_2 (30 mL) was added a solution of **12** (0.73 g, 2.30 mmol) in CH_2Cl_2 (30 mL). After 48 h of stirring at rt, the reaction mixture was filtered and the black solid washed with CH_2Cl_2 (2×). The combined organic solutions were evaporated, and the residue was purified by column chromatography (hexanes–EtOAc, 3:1, v/v) giving **13** (0.58 g, 80%, 78% ee) as an orange oil, $[\alpha]_D^{20}$=+26.4 (*c* 1, $CDCl_3$); R_f=0.58 (hexanes–EtOAc, 3:1, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (s, 3H), 1.42 (s, 3H), 1.69 (s, *J*=1.4 Hz, 3H), 1.75 (s, *J*=1.4 Hz, 3H), 3.58 (dd, *J*=10.9, 6.6 Hz, 1H), 3.67 (dd, *J*=10.9, 3.7 Hz, 1H), 4.05 (dd, *J*=6.6, 3.7 Hz, 1H), 4.06 (d, *J*=6.9 Hz, 2H), 5.36 (tqq, *J*=6.9, 1.4, 1.4 Hz, 1H), 6.56 (dd, *J*=15.8, 7.7 Hz, 1H), 6.96 (d, *J*=8.8 Hz, 1H), 7.05 (d, *J*=2.0 Hz, 1H), 7.07 (dd, *J*=8.8, 2.0 Hz, 1H), 7.34 (d, *J*=15.8 Hz, 1H), 9.63 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.1, 20.6, 25.0, 25.9, 68.1, 68.9, 74.3, 79.9, 117.1, 117.6, 120.6, 122.5, 127.0, 128.0, 137.8, 142.6, 145.5, 152.9, 193.7; MS (EI): *m*/*z* (rel. int.) 316 (100) [M^+], 248 (46), 218 (12), 217 (38), 189 (13), 175 (36), 164 (31), 163 (30), 147 (20), 136 (15), 135 (11), 107 (7), 85 (14), 69 (76), 68 (41), 67 (53), 53 (35); HRMS (EI) calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1672; Anal. calcd C, 72.13; H, 7.65; found C, 72.09; H, 7.84.

4.2.4. (*S*)-(1*E*,3*Z*)-8-(4-Bromopenta-1,3-dienyl)-2,2-dimethyl-3-(3-methyl-2-butenyloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin (14). To a suspension of

(1,1-dibromoethyl)triphenylphosphonium bromide[9] (1.90 g, 3.60 mmol) in THF (15 mL), maintained at −40 °C, was added a solution of *n*-butyl lithium (2.5 M in hexane, 1.44 mL, 3.60 mmol). After 1 h of stirring, a solution of **13** (0.58 g, 1.83 mmol) in THF (15 mL) was added and the reaction mixture warmed to rt. The stirring was continued for an additional 2 h, then the mixture was quenched with water (10 mL) and the aqueous layer extracted with EtOAc (2×). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (hexanes–EtOAc, 4:1, v/v) yielded **14** (0.30 g, 40%, 78% ee) as an orange oil, $[\alpha]_D^{20}$=+27.6 (*c* 1, $CDCl_3$); R_f=0.39 (hexanes–EtOAc, 10:1, v/v); IR (KBr): 3369br, 2979m, 2952w, 1713m, 1600w, 1503m, 1438m, 1370m, 1267s, 1225m, 1150s, 1121s, 1070m, 724s, 694m, 666w, 541s cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.47 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 2.40 (s, 3H), 3.52 (dd, *J*=7.7, 3.2 Hz, 1H), 3.99 (dd, *J*=12.5, 7.7 Hz, 1H), 4.14 (d, *J*=6.8 Hz, 2H), 4.26 (dd, *J*=12.5, 3.2 Hz, 1H), 5.35 (tqq, *J*=6.8, 1.4, 1.3 Hz, 1H), 6.35 (dq, *J*=10.0, 0.7 Hz, 1H), 6.50 (d, *J*=15.7 Hz, 1H), 6.86 (dd, *J*=15.7, 10.0 Hz, 1H), 6.86–7.07 (m, 3H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.2, 21.0, 25.9, 27.8, 29.3, 67.4, 68.8, 80.8, 82.0, 120.9, 122.0, 122.7, 123.7, 128.8, 132.1, 132.3, 132.8, 133.0, 137.6, 147.0, 151.4; MS (EI): *m/z* (rel. int.) 408 (98) [M^+, ^{81}Br], 406 (100) [M^+, ^{79}Br], 340 (15), 338 (15), 328 (9), 281 (12), 279 (14), 278 (13), 277 (35), 256 (22), 254 (22), 185 (11), 175 (43), 174 (28), 173 (16), 158 (12), 157 (36), 145 (17), 129 (21), 128 (14), 115 (14), 85 (14), 69 (100), 41 (39); HRMS (EI) calcd for $C_{21}H_{27}^{79}BrO_3$ 406.1144, found 406.1145.

4.2.5. (*S*)-(1*E*,3*Z*)-8-(4-Iodopenta-1,3-dienyl)-2,2-dimethyl-3-(3-methyl-2-butenyloxy)-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin (15). To a solution of **14** (0.16 g, 0.40 mmol) in HMPT (5 mL) were added KI (0.66 g, 4.00 mmol) and CuI (0.38 g, 2.00 mmol). The mixture was heated at 120 °C for 48 h, then cooled to rt and quenched with water (20 mL). The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with water (2×) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by column chromatography (hexanes–EtOAc, 10:1, v/v) yielded **15** (0.11 g, 63%, 78% ee) as a colourless oil; R_f=0.49 (hexanes–EtOAc, 10:1, v/v); ^1H NMR (300 MHz, $CDCl_3$) δ 1.23 (s, 3H), 1.47 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 2.59 (s, 3H), 3.52 (dd, *J*=7.7, 3.2 Hz, 1H), 3.99 (dd, *J*=12.5, 7.7 Hz, 1H), 4.06 (dd, *J*=11.6, 7.0 Hz, 1H), 4.16 (dd, *J*=11.6, 7.0 Hz, 1H), 4.25 (dd, *J*=12.5, 3.2 Hz, 1H), 5.35 (tqq, *J*=6.8, 1.4, 1.3 Hz, 1H), 6.35 (d, *J*=10.0 Hz, 1H), 6.50 (d, *J*=15.7 Hz, 1H), 6.85 (dd, *J*=15.7, 10.0 Hz, 1H), 6.88 (d, *J*=8.4 Hz, 1H), 6.97–7.06 (m, 2H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.5, 21.0, 25.3, 26.2, 29.6, 67.5, 68.8, 80.7, 82.1, 100.4, 115.1, 117.5, 120.4, 121.0, 125.5, 129.0, 131.5, 133.5, 138.0, 142.6, 142.8; MS (EI): *m/z* (rel. int.) 454 (1) [M^+], 412 (7), 340 (9), 338 (8), 290 (16), 274 (15), 263 (13), 238 (40), 236 (14), 222 (20), 221 (100), 220 (21), 218 (10), 207 (37), 205 (33), 203 (22), 191 (16), 190 (19), 189 (30), 179 (28), 165 (53), 163 (23), 154 (73), 149 (39), 137 (74), 85 (33), 83 (62), 69 (28); HRMS (EI) calcd for $C_{21}H_{27}IO_3$ 454.1005, found 454.1011.

4.2.6. Strobilurin G (1). To a solution of **15** (42.0 mg, 95 μmol) in NMP (1 mL) were added **7** (61.0 mg, 0.15 mmol), $Pd(Ph_3)_4$ (6.0 mg, 5 μmol), and CuI (14.0 mg, 73 μmol). The mixture was heated at 50 °C for 24 h under argon, then cooled to rt and quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (2×), and the combined organic layers were washed with water (2×) and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by column chromatography (hexanes–EtOAc, 5:1, v/v) furnished **1** (16.0 mg, 38%) as a colourless oil, $[\alpha]_D^{20}$=+21.3 (*c* 0.75, MeOH; corresponds to 79% ee), ref. 7b $[\alpha]_D^{20}$=+26.8 (*c* 0.75, MeOH); R_f=0.43 (hexanes–EtOAc, 3:1, v/v). IR (KBr) 3029w, 2990m, 1720s, 1633m, 1560m, 1551s, 1502s, 1450m, 1444w, 1430w, 1300s, 1272s, 1249s, 1220m, 1151m, 1125s, 1080s, 1010s, 985 (s), 972m cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 3H), 1.47 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 1.96 (s, 3H), 3.50 (dd, *J*=7.9, 3.2 Hz, 1H), 3.73 (s, 3H), 3.84 (s, 3H), 3.95 (dd, *J*=12.3, 7.9 Hz, 1H), 4.06 (dd, *J*=11.3, 6.8 Hz, 1H), 4.15 (dd, *J*=11.3, 6.8 Hz, 1H), 4.23 (dd, *J*=12.3, 3.2 Hz, 1H), 5.34 (tqq, *J*=6.8, 1.5, 1.5 Hz, 1H), 6.22 (d, *J*=10.7 Hz, 1H), 6.37 (d, *J*=15.6 Hz, 1H), 6.48 (dd, *J*=15.6, 10.7 Hz, 1H), 6.85 (d, *J*=7.9 Hz, 1H), 6.92 (dd, *J*=7.9, 2.1 Hz, 1H), 6.93 (d, *J*=2.1 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.2, 20.9, 23.8, 25.9, 27.8, 51.7, 62.0, 67.5, 68.8, 80.7, 82.1, 110.9, 120.7, 121.0, 121.7, 122.5, 125.8, 129.9, 130.5, 130.9, 133.8, 137.6, 146.9, 150.9, 159.0, 167.9; MS (EI): *m/z* (rel. int.) 442 (65) [M^+], 410 (9), 342 (11), 305 (28), 283 (10), 277 (19), 258 (22), 257 (13), 237 (11), 199 (11), 177 (16), 163 (14), 153 (20), 149 (12), 137 (12), 123 (13), 111 (15), 109 (11), 97 (22), 95 (15), 85 (25), 83 (26), 81 (14), 75 (17), 71 (28), 70 (15), 69 (100), 68 (14), 67 (25), 57 (37), 55 (32), 53 (12), 44 (21), 43 (27), 41 (62). HRMS (EI) calcd for $C_{26}H_{34}O_6$ 442.2355, found 442.2373.

4.3. Oxidative degradation of acetate 10

4.3.1. Ethyl (*S*)-3-(3-acetoxy-4,4-dimethyl-3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-yl)acrylate (10). To a solution of alcohol **9**[3a] (0.29 g, 1.00 mmol, 78% ee) in acetic anhydride (5 mL) were added pyridine (0.08 mL, 1.00 mmol) and a catalytic amount of DMAP. After 48 h at rt, the reaction mixture was diluted with EtOAc (20 mL), washed successively with 2 N HCl, 2 N NaOH, and water and dried over $MgSO_4$. Removal of solvent and column chromatography of the residue (hexanes–EtOAc, 3:1, v/v) yielded **10** (0.21 g, 62%, 78% ee) as a colourless oil, $[\alpha]_D^{20}$=+26.5 (*c* 1, $CDCl_3$); R_f=0.53 (hexanes–EtOAc, 3:1, v/v); IR (KBr) 2983m, 2939m, 2628w, 1743s, 1712s, 1637s, 1605m, 1573m, 1505s, 1463m, 1425m, 1371s, 1321m, 1265s, 1232s, 1178s, 1162s, 1118m, 1068m, 1038s, 983m, 953w, 900m, 861w, 830m, 754w, 701w, 674w, 645w, 629w, 604w, 514w, 480w cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, *J*=7.1 Hz, 3H), 1.37 (s, 6H), 2.15 (s, 3H), 4.18 (dd, *J*=13.0, 5.1 Hz, 1H), 4.24 (q, *J*=7.1 Hz, 2H), 4.30 (dd, *J*=13.0, 2.8 Hz, 1H), 5.05 (dd, *J*=5.1, 2.8 Hz, 1H), 6.30 (d, *J*=16.0 Hz, 1H), 6.94 (d, *J*=8.8 Hz, 1H), 7.09–7.16 (m, 2H), 7.56 (d, *J*=16.0 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.4, 21.0, 23.9, 26.4, 60.5, 69.3, 76.2, 79.9, 117.5, 121.3, 123.4, 124.5, 130.5, 143.6, 146.8, 152.9, 167.1, 170.3; MS (EI) *m/z* (rel. int.) 334 (100) [M^+], 292 (12), 274 (30), 259 (11), 233 (19), 219 (13), 208 (28), 175 (7), 163 (13), 127 (32), 85 (30), 67 (11), 43 (72); HRMS (EI) calcd for $C_{18}H_{22}O_6$ 334.1416, found 334.1412.

4.3.2. Oxidative degradation of 10 to (*R*)-2,3-dihydroxyisovaleric acid. To a mixture of **10** (0.19 g, 0.57 mmol, 78% ee), CCl_4 (12 mL), acetonitrile (12 mL), and water (18 mL) were added $RuCl_3$ (7.00 mg, 0.03 mmol) and $NaIO_4$ (3.65 g, 17.0 mmol). After 24 h stirring at rt, a second portion of $RuCl_3$ (7.00 mg, 0.03 mmol) was added and the stirring was continued for 72 h. After addition of isopropanol (3 mL) and $BaCl_2$ (4.00 g), the precipitate was filtered off and washed with CH_2Cl_2 (2×). The combined filtrates were acidified with 2 N HCl, extracted with CH_2Cl_2 (3×) and dried over $MgSO_4$. Then, the solvent was evaporated and the residue filtered through a short silica gel column (MeOH–$CHCl_3$, 1:20, v/v) to afford a brown oil, which was dissolved in a mixture of THF (2 mL), water (2 mL), and LiOH (15.0 mg, 0.60 mmol). After 3 h at rt, the reaction mixture was acidified with 2 N HCl and extracted with CH_2Cl_2 (3×). Evaporation of the dried ($MgSO_4$) extracts and chromatography of the residue on a silica gel column (MeOH–$CHCl_3$, 1:20, v/v) yielded 11.0 mg (14%) of (*R*)-2,3-dihydroxyisovaleric acid as a colourless oil, $[\alpha]_D^{20}=+9.5$ (*c* 0.2, 0.1 N HCl; corresponds to 78% ee), ref. 14a $[\alpha]_D^{20}=+12.1$ (*c* 0.2, 0.1 N HCl). ^{1}H NMR (300 MHz, CD_3OD) δ 1.29 (s, 3H), 1.30 (s, 3H), 3.96 (s, 1H); ^{13}C NMR (75.6 MHz, CD_3OD) δ 26.0, 26.1, 73.2, 78.8, 176.3; MS (EI): *m/z* (rel. int.) 135 (3) [M^++H], 117 (13), 99 (13), 85 (17), 83 (19), 73 (16), 59 (100), 43 (26), 41 (11).

4.4. Synthesis of strobilurin M

4.4.1. Ethyl 3-(3-hydroxy-3-isopropyl-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl)acrylate (17). To a solution of **16**[3a] (5.85 g, 20.0 mmol) in THF (100 mL) was added $SnCl_4$ (1 M solution in CH_2Cl_2, 1.00 mL, 1.00 mmol). After stirring for 2 h at rt, the reaction mixture was quenched with aqueous $NaHCO_3$ (20 mL), the precipitate filtered off and the aqueous layer extracted with EtOAc (2×). The combined extracts were washed with water, dried over $MgSO_4$ and evaporated to yield an orange oil that was purified by column chromatography (hexanes–EtOAc, 3:1, v/v). Crystallisation from EtOAc–hexanes afforded 2.57 g (44%) of pure **17** as a colourless solid, mp 77 °C; R_f=0.53 (hexanes–EtOAc, 3:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (d, *J*=7.0 Hz, 3H), 1.13 (d, *J*=7.0 Hz, 3H), 1.32 (t, *J*=7.2 Hz, 3H), 2.09 (sept, *J*=7.0 Hz, 1H), 3.16 (s, 1H, OH), 3.93 (d, *J*=10.9 Hz, 1H), 4.18 (d, *J*=10.9 Hz, 1H), 4.24 (q, *J*=7.2 Hz, 2H), 6.28 (d, *J*=15.9 Hz, 1H), 6.92 (d, *J*=8.2 Hz, 1H), 7.04 (dd, *J*=8.2, 2.1 Hz, 1H), 7.07 (d, *J*=2.1 Hz, 1H), 7.56 (d, *J*=15.9 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.4, 15.8, 16.5, 34.5, 60.5, 68.1, 96.3, 116.8, 117.2, 117.4, 122.2, 129.1, 142.0, 144.1, 144.4, 167.3; MS (EI): *m/z* (rel. int.) 292 (100) [M^+], 247 (12), 221 (13), 208 (24), 207 (13), 147 (12), 71 (23); HRMS (EI) calcd for $C_{16}H_{20}O_5$ 292.1311, found 292.1310; Anal. calcd C, 65.74; H, 6.90; found C, 66.00; H, 6.79.

4.4.2. Ethyl 3-{3-isopropyl-3-(3-methyl-2-butenyloxy)-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl}acrylate (18). To a suspension of NaH (0.14 g, 6.00 mmol) in DMF (20 mL), maintained at 0 °C, were added a solution of **17** (0.88 g, 3.00 mmol) in DMF (30 mL) and 3,3-dimethylallyl bromide (0.70 mL, 6.00 mmol). The mixture was stirred for 16 h at rt, then quenched with 2 N HCl (20 mL) and extracted with EtOAc (3×). The organic layers were washed with water (2×) and dried ($MgSO_4$). Evaporation of solvent and column chromatography of the residue (hexanes–EtOAc, 4:1, v/v) yielded **18** (0.35 g, 32%) as a yellowish oil; R_f=0.69 (hexanes–EtOAc, 3:1, v/v); IR (KBr): 3419 cm^{-1} (br), 2975m, 2934m, 2875w, 1711s, 1634s, 1598m, 1584m, 1510s, 1466m, 1432m, 1384m, 1368m, 1306m, 1265s, 1175s, 1143s, 1097m, 1041m, 1009m, 982m, 845w, 808w, 736w, 640w, 604w; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (d, *J*=6.9 Hz, 6H), 1.32 (t, *J*=7.2 Hz, 3H), 1.74 (d, *J*=1.3 Hz, 3H), 1.78 (d, *J*=1.3 Hz, 3H), 2.95 (sept, *J*=6.9 Hz, 1H), 4.24 (d, *J*=10.1 Hz, 1H), 4.25 (q, *J*=7.2 Hz, 2H), 4.27 (d, *J*=10.1 Hz, 1H), 4.59 (d, *J*=6.7 Hz, 1H), 5.50 (tsept, *J*=6.7, 1.3 Hz, 1H), 6.29 (d, *J*=15.9 Hz, 1H), 6.73 (d, *J*=8.3 Hz, 1H), 7.04 (dd, *J*=8.3, 2.0 Hz, 1H), 7.08 (d, *J*=2.0 Hz, 1H), 7.59 (d, *J*=15.9 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 14.4, 18.0 (2×), 18.3, 25.9, 37.1, 60.5, 66.1, 72.6, 111.5, 112.8, 114.2, 116.6, 119.5, 122.2, 128.8, 138.3, 144.4, 149.1, 150.0, 167.2; MS (EI): *m/z* (rel. int.) 360 (12) [M^+], 292 (100), 247 (8), 221 (13), 208 (48), 163 (12), 85 (11), 69 (39); HRMS (EI) calcd for $C_{21}H_{28}O_5$ 360.1937, found 360.1932; Anal. calcd C, 69.98; H, 7.83; found C, 69.80; H, 7.65.

4.4.3. 3-{3-Isopropyl-3-(3-methyl-2-butenyloxy)-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl}-2-propen-1-ol (19). Following the same procedure as for **11**, ester **18** (0.86 g, 2.39 mmol) was used. Column chromatography yielded pure **19** (0.70 g, 92%) as an orange oil; R_f=0.54 (hexanes–EtOAc, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J*=6.7 Hz, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 1.73 (d, *J*=1.3 Hz, 3H), 1.75–1.88 (m, 1H), 1.78 (s, *J*=1.3 Hz, 3H), 3.09 (br, 1H, OH), 3.86 (d, *J*=9.5 Hz, 1H), 4.09 (d, *J*=9.5 Hz, 1H), 4.29 (dd, *J*=5.9, 1.6 Hz, 2H), 4.55 (d, *J*=6.7 Hz, 2H), 5.49 (tsept, *J*=6.7, 1.3 Hz, 1H), 6.22 (dt, *J*=15.8, 5.9 Hz, 1H), 6.47 (dt, *J*=15.8, 1.6 Hz, 1H), 6.86 (d, *J*=7.9 Hz, 1H), 6.89 (d, *J*=1.9 Hz, 1H), 6.96 (dd, *J*=7.9, 1.9 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.3 (2×), 18.8, 25.9, 30.8, 63.8, 66.0, 73.5, 74.6, 111.7, 115.6, 119.7, 120.0, 127.1, 131.0, 131.1, 138.2, 148.7, 149.3; MS (EI): *m/z* (rel. int.) 318 (9) [M^+], 252 (100), 250 (15), 225 (56), 166 (57), 139 (38), 138 (50), 137 (20), 124 (13), 123 (41), 110 (24), 69 (81); HRMS (EI) calcd for $C_{19}H_{26}O_4$ 318.1831, found 318.1827; Anal. calcd C, 71.67; H, 8.23; found C, 71.60; H, 8.64.

4.4.4. 3-{3-Isopropyl-3-(3-methyl-2-butenyloxy)-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl}propenal (20). Following a procedure similar to that used for **12**, alcohol **19** (0.67 g, 2.10 mmol) and MnO_2 (1.80 g, 21.0 mmol) were stirred in CH_2Cl_2 (50 mL) for 48 h at rt. Column chromatography (hexanes–EtOAc, 2:1, v/v) yielded **20** (0.46 g, 69%) as an orange oil; R_f=0.69 (hexanes–EtOAc, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (d, *J*=6.9 Hz, 3H), 1.02 (d, *J*=6.9 Hz, 3H), 1.74 (d, *J*=1.4 Hz, 3H), 1.77–1.91 (m, 1H), 1.78 (d, *J*=1.4 Hz, 3H), 3.92 (d, *J*=9.5 Hz, 1H), 4.12 (d, *J*=9.5 Hz, 1H), 4.55 (d, *J*=6.7 Hz, 2H), 5.48 (tsept, *J*=6.7, 1.4 Hz, 1H), 6.58 (dt, *J*=15.8, 7.7 Hz, 1H), 6.92 (d, *J*=8.2 Hz, 1H), 7.09 (d, *J*=2.0 Hz, 1H), 7.12 (dd, *J*=8.2, 2.0 Hz, 1H), 7.39 (d, *J*=15.8 Hz, 1H), 9.64 (d, *J*=7.7 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 18.1, 18.4, 18.8, 25.9, 30.9, 66.1, 72.7, 74.5, 112.6, 114.4, 119.3, 123.4, 127.0, 127.8, 138.5, 149.4, 151.8, 152.9, 193.6; MS (EI): *m/z* (rel. int.) 316 (4) [M^+], 251 (22), 250 (100), 164 (60), 163 (16), 147 (23), 136 (13), 69 (49); HRMS (EI) calcd for $C_{19}H_{24}O_4$ 316.1675, found 316.1680; Anal. calcd C, 72.13; H, 7.65; found C, 72.09; H, 7.83.

4.4.5. (1*E*,3*Z*)-7-(4-Bromo-penta-1,3-dienyl)-2-isopropyl-2-(3-methyl-2-butenyloxy)-2,3-dihydro-2*H*-benzo[1,4]dioxin (21). Following a procedure similar to that used for **13**, aldehyde **20** (0.40 g, 1.26 mmol) yielded **21** (0.24 g, 47%) as an orange oil (column chromatography: hexanes–EtOAc, 7:1, v/v); R_f=0.49 (hexanes–EtOAc, 5:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, J=6.8 Hz, 3H), 1.02 (d, J=6.8 Hz, 3H), 1.78 (s, 3H), 1.79 (s, 3H), 1.81 (sept, J=6.8 Hz, 1H), 2.41 (s, 3H), 3.90 (d, J=9.6 Hz, 1H), 4.12 (d, J=9.6 Hz, 1H), 4.58 (m, 2H), 5.49 (tsept, J=6.7, 1.3 Hz, 1H), 6.37 (dq, J=10.0, 0.7 Hz, 1H), 6.55 (d, J=15.7 Hz, 1H), 6.84 (dd, J=15.7, 10.0 Hz, 1H), 6.87 (d, J=8.4 Hz, 1H), 6.95 (dd, J=8.4, 2.0 Hz, 1H), 7.01 (d, J=2.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 18.2, 18.4, 18.8, 25.9, 29.3, 30.8, 66.1, 73.6, 74.6, 111.6, 115.9, 119.9, 120.4, 123.5, 125.4, 128.6, 131.6, 133.5, 138.1, 149.0, 149.6; MS (EI): *m/z* (rel. int.) 408 (96) [M^+, ^{81}Br], 406 (97) [M^+, ^{79}Br], 340 (12), 338 (15), 281 (10), 279 (14), 278 (15), 277 (39), 256 (25), 254 (25), 185 (11), 175 (48), 174 (24), 157 (42), 145 (19), 129 (23), 128 (14), 115 (14), 85 (16), 69 (100), 41 (38); HRMS (EI) calcd for $C_{21}H_{27}^{79}BrO_3$ 406.1144, found 406.1138.

4.4.6. Strobilurin M (2). To a solution of **21** (0.11 g, 0.27 mmol) in HMPT (4 mL) were added KI (0.45 g, 2.70 mmol) and CuI (0.26 g, 1.35 mmol). The mixture was heated at 120 °C for 48 h, then cooled to rt, quenched with water (20 mL) and extracted with EtOAc (3×). The combined extracts were washed with water (2×) and dried over $MgSO_4$. Evaporation of the solvent yielded an orange residue (55 mg), which, after dissolving in NMP (1 mL), was treated with **7** (68 mg, 0.18 mmol), $Pd(Ph_3)_4$ (7 mg, 6.00 μmol), and CuI (3 mg, 12.0 μmmol). The reaction mixture was heated at 50 °C for 24 h and then quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (2×), and the combined extracts were washed with water (2×) and dried ($MgSO_4$). Concentration and purification of the residue by column chromatography (hexanes–EtOAc, 3:1, v/v) yielded **2** (24 mg, 19%) as a yellowish oil; R_f=0.51 (hexanes–EtOAc, 3:1, v/v); IR (KBr): 3439(br), 2937m, 1710s, 1628m, 1507s, 1433m, 1288s, 1274s, 1237m, 1120s, 991m cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, J=7.1 Hz, 3H), 1.05 (d, J=7.1 Hz, 3H), 1.48 (s, 3H), 1.62 (s, 3H), 1.95 (d, J=1.2 Hz, 3H), 2.43 (sept, J=7.1 Hz, 1H), 3.73 (s, 3H), 3.84 (s, 3H), 3.93 (d, J=11.1 Hz, 1H), 3.99 (dd, J=11.0, 6.9 Hz, 1H), 4.07 (dd, J=11.0, 7.0 Hz, 1H), 4.15 (d, J=11.1 Hz, 1H), 5.14 (tqq, J=7.0, 6.9, 1.3 Hz, 1H), 6.23 (dd, J=10.6, 1.2 Hz, 1H), 6.38 (d, J=15.6 Hz, 1H), 6.47 (dd, J=15.6, 10.6 Hz, 1H), 6.80 (d, J=8.4 Hz, 1H), 6.84 (dd, J=8.4, 2.0 Hz, 1H), 6.92 (d, J=2.0 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 16.3, 17.0, 17.6, 23.5, 25.6, 31.3, 51.5, 57.6, 61.7, 64.9, 98.9, 110.8, 114.5, 116.7, 120.5, 122.2, 124.8, 129.7, 130.2, 130.7, 131.6, 136.6, 141.6, 142.6, 158.7, 167.7; MS (EI): *m/z* (rel. int.) 442 (100) [M^+], 374 (39), 342 (17), 237 (65), 69 (60), 41 (62); HRMS (EI) calcd for $C_{26}H_{34}O_6$ 442.2355, found 442.2334.

4.5. Synthesis of strobilurin N

4.5.1. 1-Bromo-3-methyl-3-(tetrahydropyran-2-yloxy)-butan-2-one (23).[7d] To a solution of 1-bromo-3-hydroxy-3-methylbutan-2-one (**22**)[16] (4.51 g, 25.8 mmol) in CH_2Cl_2 (25 mL) were added dihydropyran (3.12 g, 37.1 mmol) and PPTS (0.62 g, 2.47 mmol). After 4 h stirring at rt, the reaction mixture was diluted with anhydrous Et_2O (30 mL) and washed with brine (2×) and water (2×). Concentration of the dried ($MgSO_4$) solution yielded pure **23** (6.05 g, 91%) as a colourless oil, bp 75 °C (7 mbar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.40 (s, 3H), 1.65–1.93 (m, 6H), 3.30–3.39 (m, 1H), 3.44–3.53 (m, 1H), 3.83–3.89 (m, 1H), 4.49 (d, J=16.5 Hz, 1H), 4.69 (d, J=16.5 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 21.3, 21.7, 25.1, 25.8, 27.3, 31.7, 65.1, 81.3, 95.9, 205.0; MS (EI): *m/z* (rel. int.) 265 (1) [M^+, ^{81}Br], 263 (1) [M^+, ^{79}Br], 251 (1), 85 (100).

4.5.2. Ethyl 3-{3-hydroxy-3-[1-methyl-1-(tetrahydropyran-2-yloxy)-ethyl]-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl}acrylate (24). To a solution of **23** (5.32 g, 20.0 mmol) in acetone (100 mL) were added ethyl 3,4-dihydroxycinnamate (4.16 g, 20.0 mmol) and K_2CO_3 (5.52 g, 40.0 mmol). The mixture was heated at 80 °C for 1 h, then a second portion of **23** (2.66 g, 10.0 mmol) was added and the heating continued for another 3 h. After cooling to rt, the reaction mixture was quenched with water (100 mL) and the aqueous layer extracted with EtOAc (3×). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated. The resulting residue was purified by column chromatography (hexanes–EtOAc, 3:1, v/v) to yield **24** (2.28 g, 29%) as a colourless oil; R_f=0.54 (hexanes–EtOAc, 5:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.47–1.93 (m, 6H), 2.03 (s, 1H, OH), 3.45–3.59 (m, 1H), 3.82–3.91 (m, 1H), 3.94–4.05 (m, 1H), 4.03 (d, J=11.0 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.34 (d, J=11.0 Hz, 1H), 6.27 (d, J=15.9 Hz, 1H), 6.91 (d, J=8.1 Hz, 1H), 7.07 (d, J=2.0 Hz, 1H), 7.08 (dd, J=8.1, 2.0 Hz, 1H), 7.55 (d, J=15.9 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.4, 19.8, 23.4, 24.3, 25.5, 30.8, 60.5, 63.0, 66.5, 73.8, 94.7, 96.5, 116.8, 117.1, 117.5, 122.5, 129.1, 141.8, 144.0, 144.4, 167.3; MS (EI): *m/z* (rel. int.) 392 (1) [M^+], 308 (94), 290 (22), 263 (32), 249 (29), 222 (77), 208 (83), 193 (66), 176 (20), 163 (41), 147 (36), 134 (23), 133 (13), 118 (8), 89 (14), 85 (100), 69 (13), 59 (64), 43 (31).

4.5.3. Ethyl 3-{3-hydroxy-3-(1-hydroxy-1-methylethyl)-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl}acrylate (25). To a solution of **24** (8.30 g, 21.0 mmol) in EtOH (200 mL) was added PPTS (0.53 g, 2.10 mmol). The mixture was heated at 90 °C for 2 h, then the solvent was evaporated and the residue purified by column chromatography (hexanes–EtOAc, 3:1, v/v) to yield **25** (3.09 g, 48%) as a colourless solid, mp 121 °C; R_f=0.16 (hexanes–EtOAc, 3:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J=7.2 Hz, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.65 (s, 1H, OH), 2.34 (s, 1H, OH), 4.03 (d, J=11.0 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 4.31 (d, J=11.0 Hz, 1H), 6.27 (d, J=16.0 Hz, 1H), 6.94 (d, J=8.0 Hz, 1H), 7.05 (d, J=1.7 Hz, 1H), 7.08 (dd, J=8.0, 1.7 Hz, 1H), 7.55 (d, J=16.0 Hz, 1H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 14.4, 23.5, 24.3, 60.5, 66.5, 73.9, 96.5, 116.8, 117.2, 117.6, 122.6, 129.1, 141.7, 144.0, 144.5, 167.3, MS (EI): *m/z* (rel. int.) 308 (100) [M^+], 290 (6), 263 (24), 249 (24), 222 (50), 208 (76), 193 (48), 163 (29), 147 (25), 134 (12), 91 (3), 89 (6), 59 (43), 43 (20); HRMS (EI) calcd for $C_{16}H_{20}O_6$ 308.1260, found 308.1257; Anal. calcd C, 62.33; H, 6.54; found C, 62.47; H, 6.57.

4.5.4. 2-(1-Hydroxy-1-methylethyl)-7-(3-hydroxypropenyl)-2,3-dihydro-2*H*-benzo[1,4]-dioxin-2-ol (26). Following a procedure similar to that used for **11**, ester **25** (0.62 g, 2.00 mmol) and a 1 M solution of DIBAL-H (4.00 mL, 6.00 mmol) in THF were used. After 24 h, the usual workup yielded an orange oil that was purified by column chromatography (hexanes–EtOAc, 1:1, v/v). Crystallisation of the product from EtOAc–hexanes afforded pure **26** (0.11 g, 20%) as a colourless solid, mp 143 °C; R_f=0.22 (hexanes–EtOAc, 1:1, v/v); ^{1}H NMR (300 MHz, [D$_6$]acetone) δ 1.34 (s, 6H), 3.78 (t, J=5.6 Hz, 1H, OH), 3.87 (s, 1H, OH), 4.09 (dd, J=11.1, 1.3 Hz, 1H), 4.19 (dd, J=5.6, 5.4 Hz, 2H), 4.27 (d, J=11.1 Hz, 1H), 5.42 (d, J=1.3 Hz, 1H, OH), 6.22 (dt, J=15.9, 5.4 Hz, 1H), 6.48 (dt, J=15.9, 1.5 Hz, 1H), 6.78 (dd, J=7.1, 1.6 Hz, 1H), 6.88 (d, J=1.6 Hz, 1H), 6.89 (d, J=7.1 Hz, 1H); ^{13}C NMR (300 MHz, [D$_6$]acetone) δ 24.2, 24.6, 63.3, 67.2, 73.8, 97.5, 115.9, 117.3, 120.3, 129.2, 129.7, 132.1, 143.2, 143.4; MS (EI): *m*/*z* (rel. int.) 266 (100) [M$^+$], 248 (5), 223 (4), 207 (22), 180 (8), 166 (28), 133 (14), 91 (10), 77 (7), 59 (50), 43 (19); HRMS (EI) calcd for $C_{14}H_{18}O_5$ 266.1154, found 266.1155.

4.5.5. 3-{3-Hydroxy-3-(1-hydroxy-1-methylethyl)-2,3-dihydro-2*H*-benzo[1,4]dioxin-6-yl}propenal (27). Following a procedure similar to that used for **12**, alcohol **26** (105 mg, 0.39 mmol) and MnO_2 (0.17 g, 1.97 mmol) were stirred in CH_2Cl_2 (10 mL) for 24 h at rt. Purification by column chromatography (hexanes–EtOAc, 1:1, v/v) and crystallisation of the product from hexanes–EtOAc afforded pure **27** (31.0 mg, 28%) as a colourless solid, mp 158 °C; R_f=0.45 (hexanes–EtOAc, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.40 (s, 3H), 4.19 (d, J=11.2 Hz, 1H), 4.36 (d, J=11.2 Hz, 1H), 6.66 (dd, J=15.8, 7.8 Hz, 1H), 6.99 (d, J=8.3 Hz, 1H), 7.24 (dd, J=8.3, 2.1 Hz, 1H), 7.29 (d, J=2.1 Hz, 1H), 7.60 (d, J=15.8 Hz, 1H), 9.61 (d, J=7.9 Hz, 1H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.5, 24.3, 66.6, 73.8, 96.5, 117.5, 117.8, 123.3, 127.3, 128.5, 141.9, 145.5, 152.5, 193.7; MS (EI): *m*/*z* (rel. int.) 264 (34) [M$^+$], 247 (3), 222 (27), 206 (30), 179 (29), 165 (69), 164 (100), 147 (46), 136 (40), 132 (31), 107 (19), 89 (20), 77 (22), 59 (95), 43 (58); HRMS (EI) calcd for $C_{14}H_{16}O_5$ 264.0998, found 264.0991; Anal. calcd C, 63.63; H, 6.10; found C, 63.50; H, 6.15.

4.5.6. (1*E*,3*Z*)-7-(4-Bromopenta-1,3-dienyl)-2-(1-hydroxy-1-methylethyl)-2,3-dihydro-2*H*-benzo[1,4]-dioxin-2-ol (28). Following a procedure similar to that used for **13**, (1,1-dibromoethyl)triphenylphosphonium bromide[9] (0.85 g, 1.60 mmol), *n*-butyl lithium (2.5 M in hexane, 0.60 mL, 1.50 mmol), and aldehyde **27** (0.40 g, 1.26 mmol) afforded after chromatography (hexanes–EtOAc, 1:1, v/v) and crystallisation from EtOAc–hexanes **28** (0.11 g, 38%) as a yellowish solid, mp 133 °C; R_f=0.68 (hexanes–EtOAc, 1:1, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.41 (s, 3H), 2.41 (s, 3H), 4.01 (d, J=11.0 Hz, 1H), 4.29 (d, J=11.0 Hz, 1H), 6.36 (dq, J=10.0, 0.7 Hz, 1H), 6.51 (d, J=15.6 Hz, 1H), 6.87 (dd, J=15.6, 10.0 Hz, 1H), 6.85–7.07 (m, 3H); ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.3, 24.3, 29.3, 66.5, 73.8, 96.5, 122.0, 122.7, 123.7, 128.8, 132.3, 132.8, 133.0, 137.6, 141.7, 147.0; MS (EI): *m*/*z* (rel. int.) 356 (46) [M$^+$, ^{81}Br], 354 (47) [M$^+$, ^{79}Br], 342 (26), 340 (28), 277 (25), 267 (25), 265 (25), 256 (18), 254 (20), 252 (21), 175 (39), 174 (34), 173 (26), 161 (33), 160 (43), 159 (25), 157 (28), 145 (25), 144 (17), 143 (22), 132 (15), 131 (31), 129 (22), 128 (21), 115 (50), 103 (12), 77 (16), 59 (100), 43 (57); HRMS (EI) calcd for $C_{16}H_{19}^{79}BrO_4$ 354.0470, found 354.0467; Anal. calcd C, 54.10; H, 5.39; Br 22.49; found C, 53.89; H, 5.33; Br 22.65.

4.5.7. Strobilurin N (3). To a solution of **28** (93.0 mg, 0.26 mmol) in HMPT (3 mL) were added KI (0.43 g, 2.60 mmol) and CuI (0.25 g, 1.30 mmol) The mixture was heated at 120 °C for 48 h, then cooled and quenched with water (20 mL). The aqueous layer was extracted with EtOAc (3×), and the combined organic layers were washed with water (2×) and dried ($MgSO_4$). Concentration yielded an orange oil (42.0 mg), which, after being dissolved in NMP (1 mL), was treated with **7** (61.0 mg, 0.15 mmol), $Pd(Ph_3)_4$ (6.00 mg, 5.00 μmol), and CuI (14.00 mg, 73.0 μmmol). The reaction mixture was heated for 24 h to 50 °C, cooled to rt and quenched with saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with EtOAc (2×), and the combined organic layers were washed with water (2×) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by column chromatography (hexanes–EtOAc, 3:1, v/v) yielded **3** (23.0 mg, 23%) as a colourless oil; R_f=0.42 (hexanes–EtOAc, 1:1, v/v); IR, ^{1}H NMR, and MS data identical with those given for the natural product[6]; ^{13}C NMR (75.6 MHz, $CDCl_3$) δ 23.2, 23.5, 24.1, 51.5, 61.8, 66.2, 73.6, 96.3, 110.7, 114.7, 117.0, 120.5, 125.4, 129.6, 130.3, 130.7, 132.6, 141.4, 141.6, 158.8, 167.8; MS (EI): *m*/*z* (rel. int.) 390 (100) [M$^+$], 358 (22), 331 (9), 253 (84), 153 (47), 121 (9), 115 (15), 91 (12), 75 (36).

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New triterpene peroxides from *Pseudolarix kaempferi*

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Abstract—The first study of the chemical constituents of the leaves of *Pseudolarix kaemferi* revealed three new triterpene peroxides, pseudolarolides Q (**1**), R (**2**), S (**3**). The stereochemical structures of these new compounds were elucidated on the basis of spectral and single-crystal X-ray analyses.

1. Introduction

The root bark of *Pseudolarix kaempferi* Gord. (Pinaceae), a plant indigenous to eastern China, is known as *tujinpi* in Chinese folk medicine, and has been used traditionally for the treatment of dermal infections caused by fungi.[1] The chemical constituents of the root bark of this plant, as well as the seeds, have been investigated, and a variety of structurally novel di- and triterpenes have been isolated. Among these, pseudolarolides A and B, both triterpene lactones, showed anti-viral activity.[2] Pseudolarolide I, an endoperoxy dilactone, as well as pseudolarolide B, were found to be cytotoxic.[3] Diterpene lactones pseudolaric acids A and B showed potent anti-fungal and cytotoxic activities.[4,5] These results stimulated our interest to search for additional novel cytotoxic and bioactive compounds from other parts of the same plant.

Furthermore, in our ongoing study of the synthesis and biological activity of pseudolaric acids A and B,[6,7] the preparation of chemical derivatives required large quantities of these compounds as starting materials. However, pseudolaric acids are not readily available because they accumulate in significant amounts only in the bark of old trees, which are rare, protected, and very valuable. Our efforts to extract pseudolaric acids from the bark of cultivated young trees yielded very little desired material.

It occurred to us that a study of the chemical constituents of the leaves of *Pseudolarix kaempferi*, a sustained plant resource that could be continuously harvested without harming the trees, has never been undertaken. Thus an investigation was initiated to examine whether the pseudolaric acids, or any of their biogenetic precursors, could be found in *Pseudolarix* leaves. It was also of interest to see if other novel and bioactive natural products would be found in the leaves. In the course of these investigations, we have isolated three new triterpene peroxides, pseudolarolides Q–S (**1**-**3**), as well as pseudolaric acids A and B, the major bioactive diterpenoids previously found in the bark. In this paper we describe the isolation and structural elucidation of **1**-**3** (Fig. 1).

2. Results and discussion

Pseudolarolide Q **1**, obtained as colorless needles, was determined to have a molecular formula of $C_{30}H_{42}O_7$ from HR-EIMS and NMR data. The ^{1}H NMR spectrum (Table 1) of **1** showed signals for two mutually-coupled vinyl protons (δ 6.27, 1H, d, J=12.4 Hz; δ 5.96, 1H, d, J=12.4 Hz), one oxygenated methine proton (δ 4.11, 1H, td, J=10.5, 5.1 Hz), two geminally coupled protons (δ 2.77, 1H, J=12.5 Hz; δ 2.18, 1H, J=12.5 Hz) corresponding to the same methylene carbon in the HSQC spectrum (δ 59.3, C-19), two methyl groups bonded to tertiary carbon centers (δ 0.89, 6.5 Hz; and δ 1.25, d, J=7.2 Hz), and four angular methyl groups (δ 1.00, 1.02, 1.40 and 1.42). The decoupled ^{13}C NMR spectrum displayed a total of thirty carbon signals, and its corresponding DEPT spectrum showed that there were 6 methyl, 8 methylene, 8 methine carbon atoms of which two were olefinic, (δ 146.1, C-1; δ 119.3, C-2) and one was oxygenated, (δ 77.6, C-16); and 8 quaternary carbons including three oxygenated quaternary carbon atoms (δ 87.5, C-9; δ 86.1, C-10; δ 84.2, C-4) and signals attributed to an ester (saturated γ-lactone, δ 179.6, C-26), an

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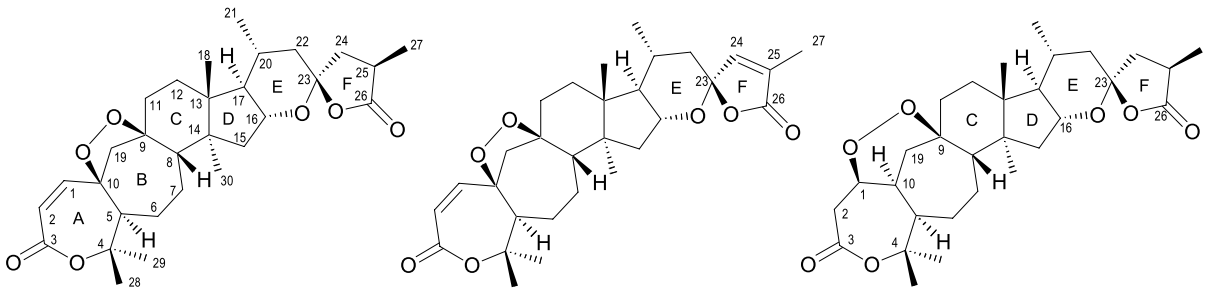

Figure 1.

α,β-unsaturated ester (unsaturated lactone, δ 166.1, C-3), and a ketal (δ 107.2, C-23) (Table 2). The IR absorptions at 1770, 1706, 1624 cm^{-1} confirmed the presence of a saturated-γ-lactone, an α,β-unsaturated lactone and alkene functionalities, respectively.

A comparison of the spectral data of **1** and pseudolarolide H (Fig. 2),[8] a 9,10-*seco*-peroxycycloartane which had undergone oxidation in ring A, showed many similarities. They have the same functional groups by IR spectroscopy, the same molecular formula and similar EI-MS fragments. Like pseudolarolide H, the EI-MS spectrum of **1** revealed a moderately strong fragment peak at *m/z* 482 $[M-O_2]^+$, characteristic of the cleavage of a peroxyl group[8] and a base peak at *m/z* 139 $[C_8H_{11}O_2]^+$, typical of a spiro ring E and saturated-γ-lactone ring F previously found in pseudolarolides A and D.[2] Together with comparable ^1H and ^{13}C NMR spectral features found in both compounds, the evidence suggests that **1** is an isomer of pseudolarolide H. This was confirmed by the following 2D NMR data. (1) The α,β-unsaturated lactone structure was supported by the HMBC correlations between H_3-28↔C-4, 5, 29; H_3-29↔C-4, 5, 28; H-2↔C-1, 3, 10; C-2, H-1↔C-3, 5, 10, 19; H-5↔C-4, 10, 19, 29. (2) The occurrence of two downfield AB doublets (δ 2.77, δ 2.18, H_2-19) is consistent with the effect of the neighboring peroxyl bridge, which was deduced to be at C-9 and C-10 due to the deshielding of the C-9 and C-10 NMR signals, and HMBC correlations between H_2-19↔C-1, 5, 8, 9, 10, 11; and H-1↔C-3, 5, 10, 19. However, in contrast to pseudolarolide H, in which the peroxyl bridge was alpha with respect to the plane of the carbon framework, NOESY correlations between H-19 (δ

Table 1. ^1H NMR chemical shift values of compounds **1**–**3**[a] (500 MHz)

Position	1	2	3
1	6.27, (d, 12.4)	6.27, (d, 12.5)	4.43, (td, 4.2, 3.8)
2α	5.96, (d, 12.4)	5.97, (d, 12.5)	3.03, (dd, 15.2, 4.8)
2β			3.10, (dd, 15.2, 4.8)
5	2.48, (dd, 10.0, 4.1)	2.47, (dd, 11.0, 4.6)	1.60–1.72, (m)
6α	2.00–2.10, (m)	2.02–2.12, (m)	2.16–2.28, (m)
6β	1.53–1.68, (m)	1.56–1.66, (m)	1.63–1.87, (m)
7α	1.52–1.69, (m)	1.52–1.69, (m)	1.44–1.54, (m)
7β	1.52–1.69, (m)	1.52–1.69, (m)	1.58–1.74, (m)
8	2.00–2.13, (m)	2.02–2.17, (m)	2.34, (dd, 12.6, 2.7)
10			2.44, (br s)
11α	1.82–1.96, (m)	1.86–1.96, (m)	1.61–1.81, (m)
11β	2.04–2.14, (m)	2.07–2.15, (m)	1.61–1.81, (m)
12α	1.58–1.70, (m)	1.65–1.73, (m)	1.60–1.67, (m)
12β	1.48–1.58, (m)	1.50–1.66, (m)	1.43–1.58, (m)
15α	1.30, (dd, 13.8, 5.3)	1.28–1.37, (m)	1.29, (dd, 13.8, 5.0)
15β	1.87, (dd, 14.0, 10.7)	1.89–1.98, (m)	1.89, (dd, 13.8, 10.5)
16	4.11, (td, 10.5, 5.1)	4.27, (td, 10.6, 5.4)	4.10, (td, 10.5, 5.0)
17	1.46, (t, 10.0)	1.45–1.56, (m)	1.48, (t, 10.4)
18	1.00, (s)	1.03, (s)	1.03, (s)
19 *exo*	2.18, (d, 12.5)	2.18, (d, 12.5)	1.69–1.76, (m)
19 *endo*	2.77, (d, 12.5)	2.77, (d, 12.5)	1.79–1.89, (m)
20	2.02–2.13, (m)	2.09–2.21, (m)	2.03–2.17, (m)
21	0.89, (d, 6.5)	0.92, (d, 6.5)	0.87, (d, 6.5)
22α	1.36–1.40, (m)	1.46–1.55, (m)	1.40, (dd, 14.0, 11.0)
22β	1.85–1.93, (m)	1.70–1.78, (m)	1.92, (dd, 14.0, 3.8)
24α	1.72, (dd, 12.4, 11.7)	6.72, (d, 1.6)	1.70, (dd, 13.0, 5.8)
24β	2.40, (dd, 12.9, 8.5)		2.40, (dd, 12.9, 8.4)
25	2.85–2.97, (m)		2.87–2.98, (m)
27	1.25, (d, 7.2)	1.91, (d, 1.6)	1.24, (d, 7.2)
28	1.42, (s)	1.41, (s)	1.58, (s)
29	1.40, (s)	1.39, (s)	1.52, (s)
30	1.02, (s)	1.03, (s)	1.05, (s)

[a] Measured in $CDCl_3$; δ in ppm, (multiplicity of signals: s, singlet; d, doublet, t, triplet; m, multiplet; br, broad, *J* in Hz).

Table 2. ^{13}C NMR chemical shift values of compounds **1**–**3**[a] (125 MHz)

Position	1	2	3
C-1	146.1 d	146.1 d	76.8 d
C-2	119.3 d	119.3 d	39.1 t
C-3	166.1 s	166.0 s	170.0 s
C-4	84.2 s	84.2 s	82.2 s
C-5	54.3 d	54.3 d	51.8 d
C-6	27.9 t	27.9 t	26.8 t
C-7	27.6 t	27.6 t	28.5 t
C-8	52.1 d	52.0 d	50.6 d
C-9	87.5 s	87.5 s	83.7 s
C-10	86.1 s	86.1 s	34.8 d
C-11	27.4 t	27.4 t	33.7 t
C-12	29.6 t	29.6 t	30.0 t
C-13	43.3 s	43.4 s	43.2 s
C-14	47.7 s	47.6 s	48.3 s
C-15	40.4 t	40.5 t	41.4 t
C-16	77.6 d	79.0 d	77.3 d
C-17	55.2 d	54.9 d	55.9 d
C-18	17.8 d	17.8 q	18.4 q
C-19	59.3 t	59.3 t	40.1 t
C-20	30.0 t	30.3 t	30.1 d
C-21	19.2 q	19.5 q	19.1 q
C-22	44.1 t	42.3 t	44.3 t
C-23	107.2 s	106.7 s	107.2 s
C-24	42.7 t	146.8 d	42.8 t
C-25	34.2 d	132.3 s	34.1 d
C-26	179.6 s	171.8 s	179.5 s
C-27	15.0 q	10.5 q	14.9 q
C-28	21.3 q	21.3 q	26.5 q
C-29	30.6 q	30.6 q	30.3 q
C-30	21.9 q	22.0 q	22.2 q

[a] Measured in $CDCl_3$; δ in ppm.

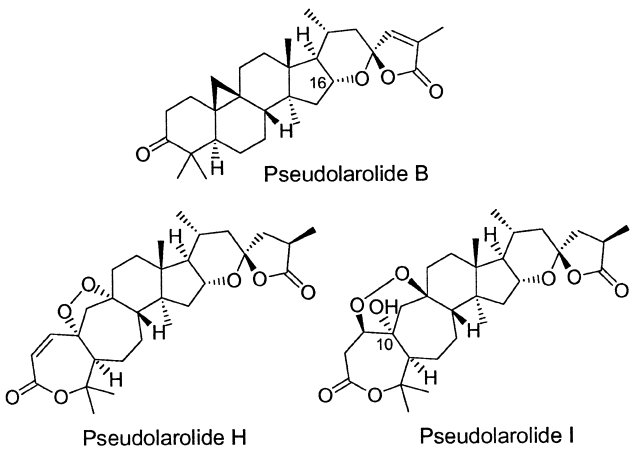

Figure 2.

2.77) with H-5, H_3-30, H-7α clearly showed that these protons were on the same face. Thus the peroxyl bridge in **1** was deduced to be in a β-orientation instead as shown in Figure 1, and the structure of **1** was unequivocally confirmed by X-ray crystallographic analysis (Fig. 3).

Pseudolarolide R **2**, obtained as colorless needles by recrystallization from acetone and ethanol, has the molecular formula $C_{30}H_{40}O_7$, as determined by HR-EI-MS ($[M]^+$ 512.2773) and NMR spectroscopy. The NMR data of **2** were very similar to those of **1**, suggesting that **2** was closely-related in structure. The major difference was that **2** had an additional degree of unsaturation. A detailed comparison of the ^1H and ^{13}C NMR signals of **1** and **2** (Tables 1 and 2) reveal that the signals due to H_2-24 (δ 2.40, 1.72), H_3-27 (δ 1.25 d, J=7.2 Hz), C-24 (δ 42.7), C-25 (δ 34.2) and C-27 (δ 15.0) of **1** have been replaced by signals due to a vinyl proton (δ 6.72, 1H, d, J=1.6 Hz, H-24), a vinyl methyl group (δ 1.91, 3H, d, J=1.6 Hz, H_3-27), alkene carbons (δ 146.8, C-24; δ 132.3, C-25) and vinyl methyl carbon signals (δ 10.5, C-27) in the spectra of **2**. Comparing their EI-MS spectra, whereas a base peak of m/z 139 was characteristic of rings E and F in **1**, the corresponding peak appeared at m/z 137 $[C_8H_9O_2]^+$ for **2**, which was characteristic of spiroannulated ring F being an α,β-unsaturated-γ-lactone in other pseudolarolides, such as pseudolarolide B (Fig. 2).[2] This was confirmed by the close correspondence in the chemical shifts of the ^{13}C NMR signals of ring F in **2** compared with that in pseudolarolide B, and the HMBC correlations H_3-27↔C-24, 25, 26; H-24↔C-23, 25, 26, 27. The distinguishing IR absorptions of **2** confirmed the presence of an unsaturated γ-lactone at 1766 cm^{-1}; α,β-unsaturated lactone at 1704 cm^{-1} and an olefin at 1626 cm^{-1}. The structure was unequivocally determined by X-ray crystallographic analysis and a perspective view of **2** is presented in Figure 4.

Pseudolarolide S **3**, obtained as colorless plates by recrystallization from acetonitrile, has a molecular formula of $C_{30}H_{44}O_7$ as determined by HR-EI-MS ($[M]^+$ 516.3087) and NMR data. The IR absorptions of **3** (1775 and 1720 cm^{-1}) indicated the presence of a saturated-γ-lactone and an ester functional group. The ^1H NMR spectrum of **3** showed signals for two oxygenated methine protons (δ 4.43, 1H, td, J=4.2, 3.8 Hz and δ 4.10, 1H, td, J=10.5, 5.0 Hz), two methyl groups on methine carbons (δ 0.87, d, J=6.5 Hz and δ 1.24, d, J=7.2 Hz) and four angular methyl groups (δ 1.03, 1.05, 1.52 and 1.58) (Table 1). The ^{13}C NMR and the corresponding DEPT spectra exhibited thirty carbon signals, consisting of 6 methyl, 9 methylene, 8 methine carbon atoms, of which two were oxidized, (δ 76.7, C-1; δ 77.3, C-16); and 7 quaternary carbon atoms, of which two were oxidized (δ 82.2, C-4, δ 83.7, C-9), as well as signals attributed to two ester groups (δ 179.5, C-26; δ 170.0, C-3), and a ketal (δ 107.2, C-23) (Table 2). The appearance of the base peak at m/z 139 in the EI-MS spectrum, together with the lack of any cyclopropyl group signals as found in pseudolarolide B, suggested that **3** was also an oxidized 9,10-*seco*-cycloartane lactone having the same spiroannulated rings E and F as found previously in **1**.

The IR, ^1H NMR and ^{13}C NMR data of **3** were found to be very similar to those of pseudolarolide I (Fig. 2)[3] and a detailed comparison indicated the two compounds have the same rings C to F. The most prominent differences between **3** and pseudolarolide I are that the former compound lacked a free hydroxyl group absorption in the IR spectrum and a methine carbon atom (δ 34.8) appeared instead of an oxidized quaternary carbon C-10 which was found in pseudolarolide I. The ^1H–^1H COSY and HSQC spectra of **3** showed that rings A and B contained a fragment –CH_2–CH(O)–$CH(CH_2)$–CH–CH_2–CH_2–CH– ascribed to C-2,

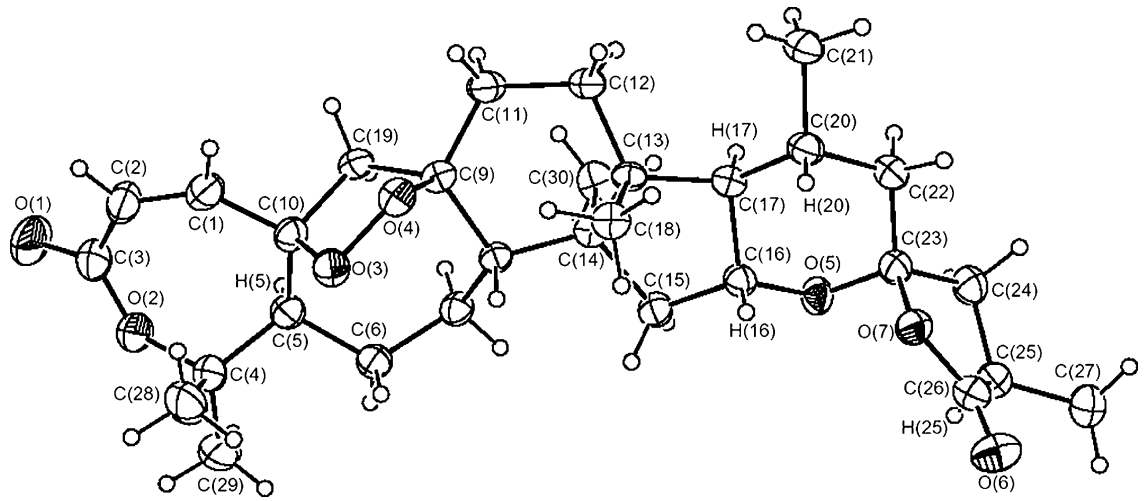

Figure 3. A perspective view of pseudolarolide Q **1**.

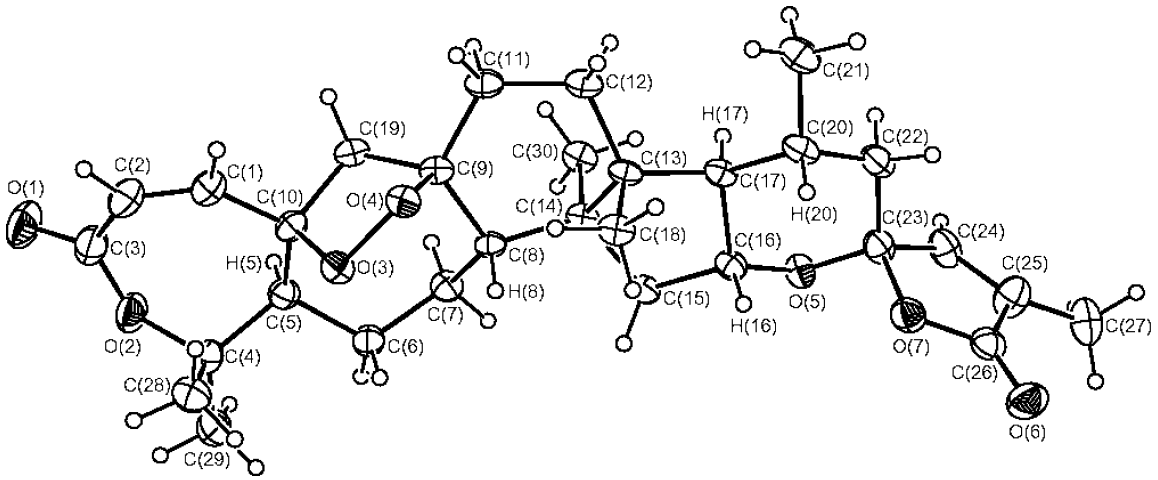

Figure 4. A perspective view of pseudolarolide R **2**.

1, 10, 19, 5, 6, 7 and 8, respectively. This suggested that **3** is 10-deoxy-pseudolarolide I, which was further confirmed by HMBC correlations between H_3-28↔C-4, 5, 29; H_3-29↔C-4, 5, 28; H_2-2↔C-1, 3, 10; H-1↔C-2, 3, 5; H-5↔C-1, 19, 29; H-10↔C-2, 4, 9, 19. Finally, the structure and stereochemistry of **3** were determined by X-ray crystallographic analysis and a perspective view of the structure of **3** is presented in Figure 5.

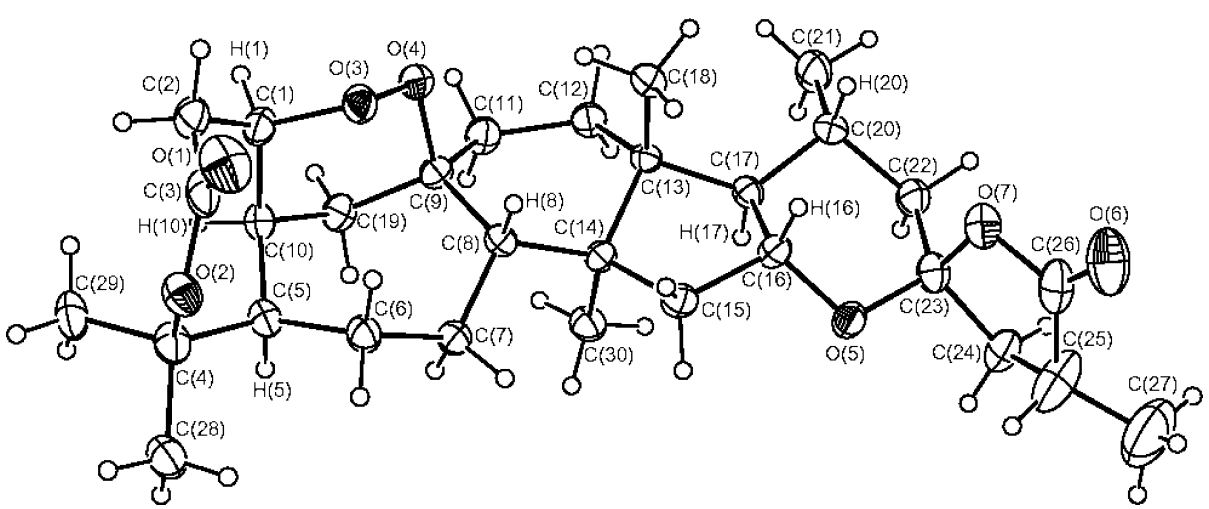

Figure 5. A perspective view of pseudolarolide S **3**.

3. Conclusions

We have isolated and identified three new peroxy triterpenoids pseudolarolides Q, R, S (**1**-**3**) in the first study of the chemical constituents of the leaves of *Pseudolarix kaemferi*. Because **3** is closely related to the cytotoxic pseudolarolide I in structure, the newly identified compounds are being studied and evaluated for bioactivity.

4. Experimental

4.1. General procedures

Melting points were uncorrected. FT-IR spectra were recorded on a Nicolet-Magna 750 spectrophotometer. NMR spectra were obtained on a Bruker 500 MHz DRX NMR spectrometer. Both LRMS and HRMS spectra were recorded on a Finnigan MAT-95 instrument.

Crystallographic data collections were made on a MAR Imaging Plate diffractometer. The crystal structure was solved by direct methods employing SIR-97 program[9] on PC and refined by full-matrix least-squares refinements using program SHELXL-97[10] on PC.

4.2. Plant material

The leaves of *Pseudularix kaempferi* were collected in December, 2002 at Linan, Zhejiang Province, P.R. China and identified by Professor Bingyang Ding of the College of Agricultural Science, Zhejiang University. A voucher specimen has been deposited at the Herbarium of the College of Agricultural Science, Zhejiang University.

4.3. Extraction and isolation

Powdered plant materials (8.0 kg) were extracted with 95% ethanol three times at room temperature. The combined residue (980 g), after removal of the solvent, was extracted by chloroform eight times. The extract was evaporated to give a black mass (400 g), which was applied on a silica gel column, eluting with light petroleum ether/$CHCl_3$ (4:1), $CHCl_3$, and $CHCl_3$ containing increasing amounts of MeOH. Repeated column chromatography yielded **1** (50 mg), **2** (18 mg) and **3** (118 mg) from the $CHCl_3$/MeOH (40:1) fractions.

4.4. Pseudolarolide Q (1)

4.4.1. Crystal data.[11] $C_{30}H_{42}O_7$, M=514.64, monoclinic, space group $P2_1$, a=6.764(1) Å, b=12.042(2) Å, c=16.776(3) Å, β=90.15(3)°, V=1366.4(4) Å^3, Z=2, D_c=1.251 g cm^{-3}, μ (Mo K_α)=0.088 mm^{-1}, F(000)=556, T=253 K; crystal dimensions: 0.30×0.15×0.10 mm. All 3570 independent reflections (R_{int}[12]=0.0352, 2808 reflections>4$\sigma(F_o)$) from a total 5372 reflections participated in the full-matrix least-square refinement against F^2. In the final stage of least-squares refinement, all non-hydrogen atoms were refined anisotropically. Convergence ($(\Delta/\sigma)_{max}$=0.001, av. 0.001) by full-matrix least-squares refinement on F^2 reaches to R_1=0.0368 and wR_2=0.1008 with a goodness-of-fit of 0.995.

Mp: 244–246 °C, $[\alpha]_{20}^{D}$ −82° (c 0.58, $CHCl_3$); IR (KBr) ν_{max}: 2956, 2869, 1770, 1706, 1624, 1442, 1384, 1307, 1231, 1110, 972, 891, 765, 599 cm^{-1}. HR-EI-MS: m/z 514.2920 $[M]^+$ (Calcd 514.2931), EI-MS: m/z (rel. Int.): 514 $[M]^+$ (12), 499 $[M-CH_3]^+$ (10), 482 $[M-O_2]^+$ (70), 470 (55), 454 (32), 439 (8), 424 (6), 399 (8), 367 (5), 343 (6), 301 (6), 249 (11), 139 (100), 121 (35), 95 (80), 81 (28), 69 (55), 55 (28). ^{1}H and ^{13}C NMR data: see Tables 1 and 2.

4.5. Pseudolarolide R (2)

4.5.1. Crystal data.[11] $C_{30}H_{40}O_7$, M=512.62, monoclinic, space group $P2_1$, a=6.700(1) Å, b=11.714(2) Å, c=16.861(3) Å, β=93.34(3)°, V=1321.1(4) Å^3, Z=2, D_c=1.289 g cm^{-3}, μ (Mo K_α)=0.090 mm^{-1}, F(000)=552, T=253 K; crystal dimensions: 0.7×0.4×0.15 mm. All 3501 independent reflections (R_{int}[12]=0.0324, 2809 reflections>4$\sigma(F_o)$) from a total 6657 reflections participated in the full-matrix least-square refinement against F^2. In the final stage of least-squares refinement, all non-hydrogen atoms were refined anisotropically. Convergence ($(\Delta/\sigma)_{max}$=0.001, av. 0.001) by full-matrix least-squares refinement on F^2 reaches to R_1=0.0332 and wR_2=0.0800 with a goodness-of-fit of 0.996.

Mp: 219–221 °C, $[\alpha]_{20}^{D}$ −90° (c 0.53, $CHCl_3$); IR (KBr) ν_{max}: 2956, 2923, 1766, 1704, 1630, 1386, 1303, 973, 891, 769, 597 cm^{-1}. HR-EI-MS: m/z 512.2773 $[M]^+$ (Calcd 512.2774), EI-MS: m/z (rel. Int.): 512 $[M]^+$ (6), 480 $[M-O_2]^+$ (5), 358 (5), 303 (6), 227 (6), 204 (21), 150 (15), 149 (11), 137 (100), 131 (11), 119 (22), 111 (12), 105 (15). ^{1}H and ^{13}C NMR data: see Tables 1 and 2.

4.6. Pseudolarolide S (3)

4.6.1. Crystal data.[11] $C_{30}H_{44}O_7$, M=516.65, orthorhombic, space group $P2_12_12_1$, a=12.561(3) Å, b=13.515(3) Å, c=16.354(3) Å, V=2776.3(10) Å^3, Z=4, D_c=1.236 g cm^{-3}, μ (Mo K_α)=0.086 mm^{-1}, F(000)=1120, T=253 K; crystal dimensions: 0.5×0.3×0.2 mm. All 3514 independent reflections (R_{int}[12]=0.0458, 2426 reflections>4$\sigma(F_o)$) from a total 10652 reflections participated in the full-matrix least-square refinement against F^2. In the final stage of least-squares refinement, all non-hydrogen atoms were refined anisotropically. Convergence ($(\Delta/\sigma)_{max}$=0.001, av. 0.001) by full-matrix least-squares refinement on F^2 reaches to R_1=0.0383 and wR_2=0.0803 with a goodness-of-fit of 0.879.

Mp: 233–234 °C, $[\alpha]_{20}^{D}$ −33° (c 0.85, $CHCl_3$); IR (KBr) ν_{max}: 2955, 2923, 1775, 1721, 1279, 768 cm^{-1}. HR-EI-MS: m/z 516.3087 $[M]^+$ (Calcd 516.3087), EI-MS: m/z (rel. Int.): 516 $[M]^+$ (10), 481 (10), 471 (19), 454 (18), 439 (19), 413 (25), 403 (31), 250 (16), 175 (12), 159 (15), 153 (15), 151 (8), 139 (100), 133 (8), 121 (29). ^{1}H, ^{13}C NMR data: see Tables 1 and 2.

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11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 226711, 226712, 226713.
12. $R_{\text{int}}=\sum|F_o^2-F_o^2(\text{mean})|/\sum[F_o^2]$.