Thieme Chemistry Journal Awardees – Where Are They Now? Stereoselective Synthesis of *Z*-Configured α,β-Unsaturated Macrocyclic Lactones and Diolides by Intramolecular Julia–Kocienski Olefination

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Received 15 October 2009

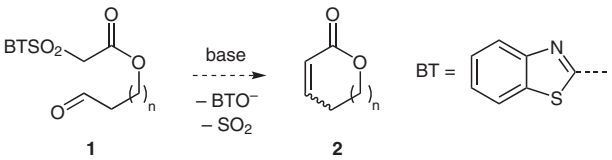
Abstract: ω-Sulfonyl aldehydes derived from the esterification of (benzothiazol-2-ylsulfonyl)acetic acid with either ω-alkenols or α,ω-diols, followed by ozonolysis or Dess–Martin oxidation as appropriate, underwent intramolecular Julia–Kocienski olefination when treated with DBU. Macrocyclic α,β-unsaturated lactones of between 12- and 19-membered ring sizes were formed successfully using this tactic (24–44% yield, *Z*/*E* ≥ 3.5:1); however, diolides were selectively produced from precursors intended to target seven- to nine-membered-ring lactones (13–70% yield, *ZZ*/*ZE* ≥ 2:1).

Key words: olefination, macrocycles, lactones, alkenes, sulfones

It was recently reported that α,β-unsaturated esters are conveniently generated from aldehydes by treatment with ethyl (benzothiazol-2-ylsulfonyl)acetate (**4**) under mild conditions (DBU, CH_2Cl_2, ≤20 °C).[1] Enoate formation presumably occurs via the commonly accepted mechanism for the Julia–Kocienski olefination,[2] and *Z*-configured products are obtained selectively from unbranched aliphatic aldehydes (*Z*/*E* up to 92:8 at –78 °C). Zajc and Lequeux later independently disclosed that α-fluorinated analogues of **4** yield valuable α-fluoroacrylate derivatives in excellent yield,[3] further highlighting the good utility of benzothiazol-2-yl (BT) sulfone based alternatives to the HWE reaction.[4,5] Given a preponderance of α,β-unsaturated lactones among biologically active secondary metabolites,[6] and the ease of alkene formation from BT-sulfonyl acetates, realization of an effective intramolecular variant of this new type of enoate synthesis would constitute a worthwhile advance. To date, surprisingly little attention has been directed toward study of the intramolecular Julia–Kocienski olefination. Of note, Leahy and co-workers reported a failed attempt to conclude their synthesis of rhizoxin D using such a tactic.[7] More recently, Aïssa successfully demonstrated the formation of unsaturated carbocycles by heating 1-*tert*-butyl-1*H*-tetrazol-5-yl sulfones[8] with tethered aldehyde functionality in the presence of Cs_2CO_3 as base in THF–DMF solvent (at 65 °C).[9] Herein, we report our own findings relating to the nascent intramolecular Julia–Kocienski olefination and describe the first examples of α,β-unsaturated lactone synthesis via base-mediated cyclization of ω-sulfonyl aldehydes **1** (Scheme 1).[10]

SYNLETT 2010, No. 3, pp 0374–0378
Advanced online publication: 11.01.2010
DOI: 10.1055/s-0029-1219185; Art ID: S12009ST

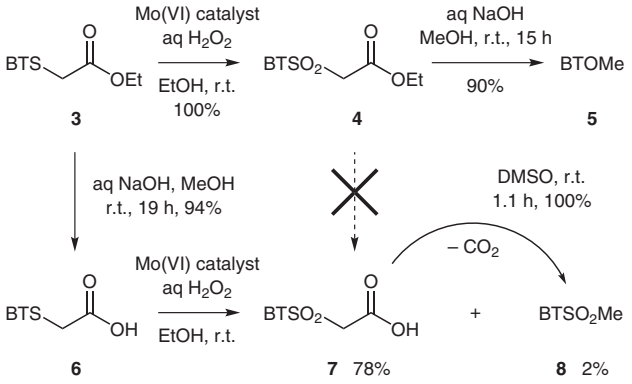
Paul R. Blakemore was born in London, England, in 1973. He was inspired to build a career in organic chemistry after an early internship at Rhône-Poulenc (now Sanofi-Aventis) revealed the creative possibilities of chemical synthesis. Upon leaving high school, Paul pursued BSc degrees in chemistry and mathematics from the University of Southampton (UK) and later joined the research group of Professor Philip J. Kocienski, then at Southampton, to undertake graduate work in the field of sulfone-based olefination methods. The Kocienski group relocated to the University of Glasgow in 1996, and it was there that Paul discovered that *trans*-alkenes can be made with high levels of stereocontrol from 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones. This variant of the Julia–Kocienski olefination has since become a very popular tactic for the synthesis of complex molecules. An enjoyable period of post-doctoral research then followed within the laboratories of Professor James D. White at Oregon State University in Corvallis, Oregon, USA. During this time (1999–2001), Paul worked on many projects and had the good fortune to conclude group efforts that culminated in total syntheses of several alkaloid and polyketide targets. With a productive post-doctoral stint behind him, Paul was awarded a fellowship from the Royal Society which enabled a temporary return to the UK and the commencement of an independent research career at the University of Leeds. Paul was soon enticed back to the wonders of the Pacific Northwest, however, and he has been a member of the chemistry faculty at Oregon State University since 2005. Research in the Blakemore laboratory is focused on the development of new synthetic methods for the absolute control of molecular constitution and stereochemistry.



Scheme 1 Focus of study: formation of α,β-unsaturated lactones **2** via intramolecular Julia–Kocienski olefination from ω-sulfonyl aldehydes **1**

The ω-sulfonyl aldehydes of interest were targeted via ozonolysis of the corresponding terminal olefin or else via

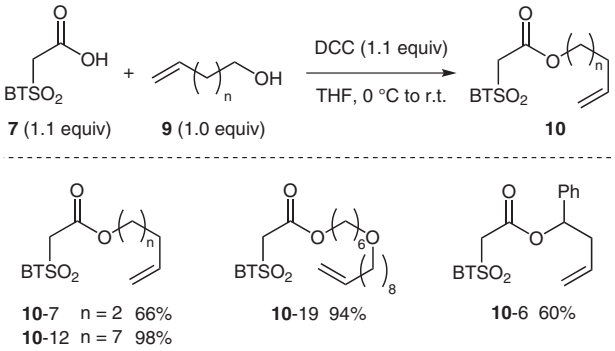
oxidation of the primary alcohol (vide infra). Access to the necessary aldehyde precursors was sought by esterification of (benzothiazol-2-ylsulfonyl)acetic acid (**7**) with an appropriate ω-alkenol or α,ω-diol. Few reports of acid **7** exist in the literature and attempts to synthesize this material by saponification of sulfonyl ester **4**[1] in methanol led to *ipso* attack upon the heterocyclic sulfone and the generation of BTOMe (**5**, Scheme 2).[11] By contrast, hydrolysis of sulfanyl ester **3** under otherwise identical conditions gave the expected free acid **6** in excellent yield. Sulfoxidation of thioether **6** to sulfone **7** has been previously reported on a small scale with $KHSO_5$,[12] but we obtained superior results using a Mo(VI)-catalyzed H_2O_2-mediated oxidation.[13] Samples of acid **7** prepared in this manner are invariably associated with trace quantities of decarboxylation adduct **8**; however, this innocuous contaminant does not interfere with subsequent steps. It was established that sulfonyl acid **7** is shelf-stable for prolonged periods (several months) in the solid state, but that this material spontaneously decarboxylates in solution. The rate of CO_2 loss was found to be sensitive to solvent polarity. Thus, in DMSO solution (at 0.05 M) complete decarboxylation of acid **7** occurred in 1.1 hours at room temperature, while the same process in acetone solution (at 0.05 M) required 22 hours at room temperature to attain full conversion.



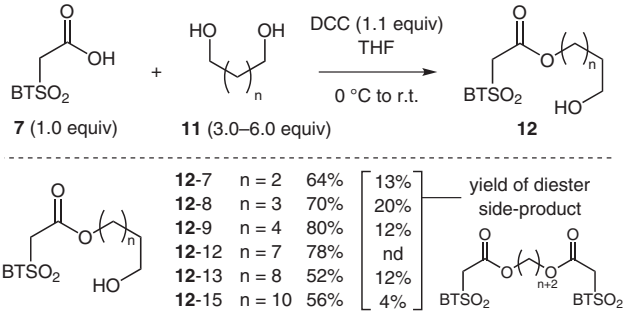
Mo(VI) catalyst = $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (10–20 mol%)

Scheme 2 Synthesis of (benzothiazol-2-ylsulfonyl)acetic acid (**7**)

With a convenient method to access acid **7** secured, the synthesis of its alkenyl ester derivatives was investigated (Scheme 3). Carbodiimide coupling of **7** with ω-alkenols **9** proceeded uneventfully to give the expected alkenyl esters in generally excellent yield.[14] Interestingly, attempts to similarly esterify sulfanyl acid **6** using DCC failed and resulted in the formation of a purple pigment tentatively attributed to be a thiazo[2,3-*b*]benzothiazolium species.[15] To concisely access a selection of carbinol-based sulfonyl aldehyde precursors, acid **7** was directly coupled to unprotected straight-chain α,ω-diols **11** using DCC as before (Scheme 4).[16] To limit the amount of anticipated diester side-product generated in these reactions, a modest excess of diol (3–6 equiv) was employed; if desired, the unreacted glycol could be recovered during purification of the reaction mixture.



Scheme 3 Synthesis of alkene-based aldehyde precursors

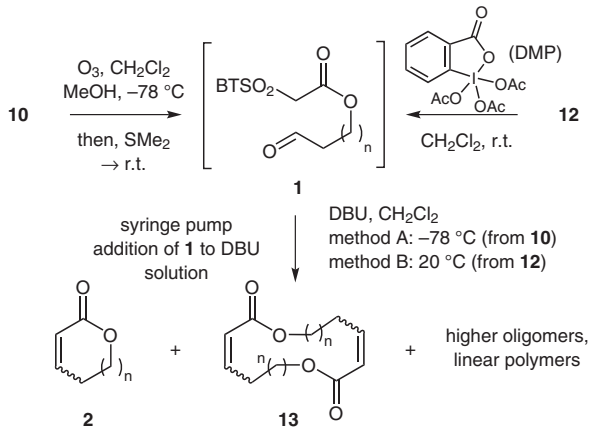


Scheme 4 Synthesis of carbinol-based aldehyde precursors

For our initial evaluation of the Julia–Kocienski process, ω-sulfonyl aldehydes **1** were generated from alkenyl BT-sulfones **10** by ozonolysis with dimethylsulfide workup. In general, the aldehydes exhibited limited stability and best results were obtained by avoiding chromatographic purification prior to their immediate deployment in base-induced cyclization. To minimize undesired intermolecular couplings, olefination was conducted using modestly high dilution with a syringe-pump addition of the freshly prepared aldehyde to a solution of DBU base in CH_2Cl_2 at –78 °C.[17] Under these conditions (method A, Table 1), only aldehyde precursor **10**-19, targeting a 19-membered lactone, led to the desired enoate product (entry 10). The yield of intramolecular olefination was acceptable when considering the large ring size generated and the absence of cyclization inducing substituents,[18] and a good preference for the (*Z*)-enoate was noted.[19] Precursors **10**-7 and **10**-12 afforded diolides **13** rich in the *Z*,*Z*-stereoisomer instead of simple lactone products (entries 2 and 6),[20] while the aldehyde derived from **10**-6 experienced facile β-elimination upon exposure to DBU and did not give a lactone nor a diolide product (entry 1).

In the second phase of the investigation, ω-sulfonyl aldehydes **1** were generated from hydroxy BT-sulfones **12** by treatment with the Dess–Martin periodinane (DMP).[21] Clean and essentially complete conversion was typically achieved in less than 1 hour at room temperature, and following a simple workup procedure, the aldehyde sub-

Table 1 Synthesis of α,β-Uunsaturated Lactones **2** and Diolides **13** by Intramolecular Julia–Kocienski Olefination from Sulfonyl Aldehydes **1**



Entry	Precursor[a]	Method[b]	Lactone **2**[19]		Diolide **13**[20]	
			Yield (%)	*Z*/*E*	Yield (%)	*ZZ*/*EZ*
1[c]	**10**-6	A	0	–:–	0	–:–
2	**10**-7	A	0	–:–	31	85:15
3[d]	**12**-7	B	0	–:–	27	89:11
4	**12**-8	B	0	–:–	70	67:33
5	**12**-9	B	0	–:–	13	63:37
6	**10**-12	A	<5	–:–	44	65:35
7	**12**-12	B	44	87:13	21	77:23
8	**12**-13	B	24	78:22	<5	–:–
9	**12**-15	B	25	80:20	<5	–:–
10[e]	**10**-19	A	43	85:15	<5	–:–

[a] Aldehyde precursor, suffix indicates ring size of target lactone.
[b] Method A: 0.02 M soln of **1** (prepared from **10** with O_3/SMe_2) added via syringe pump during 14–18 h to 0.04 M soln of DBU at –78 °C then warmed to r.t. (see ref. 17); method B: as for A except **1** (prepared from **12** with DMP) added to DBU soln at r.t. (see ref. 22).
[c] Cinnamaldehyde only significant product (36%).
[d] Olefination at r.t. led to decomposition, DBU initiated cyclization conducted instead at –78 °C with a 15 min addition period.
[e] Product is 1,13-dioxacyclononadec-3-en-2-one.

strates were directly added via syringe pump to a DBU solution. To increase the rate of intramolecular reaction and thus suppress the formation of diolides and higher oligomeric products, the cyclization was now conducted at ambient temperature (method B).[22] In again targeting the formation of **2**-12, this change had the desired effect, and the lactone was now favored over the diolide (entry 7 vs. 6). Using the same procedure, other large ring-sized *Z*-configured α,β-unsaturated lactones were also formed (entries 8 and 9); however, attempts to generate seven- to nine-membered lactones gave (*Z*,*Z*)-diolides selectively with no trace of the simple lactone products (entries 3–5). It is speculated that only larger ring sizes can readily accommodate the bond-rotation events necessary for alkene formation via the usual Julia–Kocienski pathway.[2d,e] Besides being difficult to form because of transannular strain, seven- to nine-membered cyclic β-alkoxysulfone intermediates **14** are likely to experience retroaddition (then intermolecular addition) rather than follow the usual Smiles rearrangement–anti-β-elimination pathway (**14** → **15** → **16** → **2**) that characterizes this type of olefination (Figure 1).

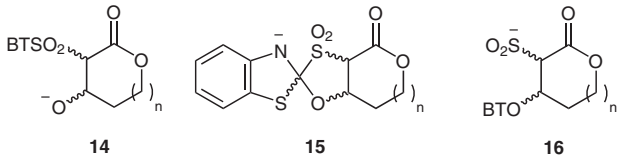


Figure 1

In conclusion, it has been demonstrated that intramolecular Julia–Kocienski olefination is a viable synthetic tactic for the elaboration of large-ring-sized α,β-unsaturated lactones. By contrast, the same process leads selectively to diolides when medium-ring-sized enoates are targeted. The method is of comparable efficiency to analogous Wittig-based protocols for macrocycle synthesis,[10] while offering stereocomplementary access to *Z*- rather than *E*-configured products. A distinguishing feature of the chemistry reported herein is the ease with which the requisite ω-sulfonyl aldehyde substrates are synthesized. The shelf-stable sulfonyl acid **7** engages in high yielding esterification with alcohols using a carbodiimide reagent and an aldehyde function may be expressed in the resulting ester product by standard methods (e.g., ozonolysis or Dess–Martin oxidation). Thus, sulfonyl acid **7** may be regarded as a convenient lynch pin capable of conjoining [about a (*Z*)-enoate linkage] the termini of suitably functionalized *seco* precursors via a short sequence of transformations. It is conceivable that the cyclization process described herein could be successfully employed in more complex scenarios.

Acknowledgment

Oregon State University is thanked for generous financial support.

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(13) **(Benzothiazol-2-ylsulfonyl)acetic Acid (7)**
A solution of sulfanyl acid **6** (2.18 g, 9.68 mmol)[12] in EtOH (90 mL) at 0 °C was treated with $(NH_4)_6Mo_7O_{24}·4H_2O$ (1.20 g, 0.971 mmol) and stirred for 5 min. 30 wt% aq H_2O_2 (67 mL, 656 mol) was then added during 3 min, and the mixture allowed to warm to r.t. and stirred for 17 h. After this time, the reaction mixture was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL) and the layers separated. The aqueous phase was extracted with CH_2Cl_2 (6 × 20 mL) and the combined organic phases washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), and concentrated in vacuo (bath temperature 25 °C) to afford sulfonyl acid **7** (1.99 g, 98 wt% remainder **8**, 7.58 mmol, 78%) as a colorless solid; mp 131–133 °C. IR (KBr): 3410, 2994, 1725, 1471, 1338, 1166 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 8.31 (1 H, dd, *J* = 7.3, 1.5 Hz), 8.24 (1 H, dd, *J* = 7.7, 1.6 Hz), 7.75 (1 H, td, *J* = 7.2, 1.3 Hz), 7.71 (1 H, td, *J* = 7.2, 1.2 Hz), 4.82 (2 H, s) ppm. ^{13}C NMR (75 MHz, acetone-d_6): δ = 167.0, 163.4, 153.4, 137.7, 129.1, 128.7, 125.9, 123.9, 59. 2 ppm. Methyl sulfone **8** (2 wt%) revealed by δ_H = 3.50 (3 H, s) ppm. Any attempts to recrystallize, or otherwise purify, sulfonyl acid **7** led to further unwanted decarboxylation and increased levels of **8**. Formation of the peroxyacid derivative of **7** was not observed.

(14) **Representative Procedure: DCC Coupling of Acid 7 and 9-Decen-1-ol (Scheme 3)**
A stirred solution of acid **7** (6.80 g, 98 wt%, 25.9 mmol) in anhyd THF (200 mL) at 0 °C under Ar was treated with neat 9-decen-1-ol (3.93 g, 25.1 mmol) followed by DCC (5.72 g, 27.7 mmol). The resulting mixture was allowed to warm to r.t. and stirred for 19 h. After this time, precipitated DCU was removed by filtration and the filtrate concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 10% Et_2O in hexanes) to afford alkenyl ester **10**-12 (9.72 g, 24.6 mmol, 98%) as a pale yellow oil: IR (neat): 2929, 1738, 1639, 1471, 1346, 1157 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (1 H, dm, *J* = 7.5 Hz), 8.02 (1 H, dm, *J* = 7.1 Hz), 7.66 (1 H, td, *J* = 7.2, 1.4 Hz), 7.61 (1 H, td, *J* = 7.2, 1.4 Hz), 5.81 (1 H, ddt, *J* = 17.1, 10.3, 6.6 Hz), 4.99 (1 H, dm, *J* = 17.2 Hz), 4.94 (1 H, dm, *J* = 10.2 Hz), 4.58 (2 H, s), 4.10 (2 H, t, *J* = 6.6 Hz), 2.03 (2 H, q, *J* = 6.9 Hz), 1.56–1.43 (2 H, m), 1.40–1.28 (2 H, m), 1.27–1.10 (8H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.2, 161.8, 152.6, 139.2, 137.1, 128.4, 127.9, 125.7, 122.5, 114.4, 67.0, 58.9, 33.9, 29.8, 29.3, 29.1, 29.0, 28.3, 25.7 ppm. HRMS (FAB^+): *m/z* calcd for $C_{19}H_{26}NO_4S_2$: 396.1303; found: 396.1309. All other alkenyl sulfones in Scheme 3 were similarly characterized and gave comparable spectral signatures.

(15) Thiazo[2,3-*b*]benzothiazolium species have been previously identified following treatment of **6** with certain electrophilic activators. For examples, see: (a) Duffin, G. F.; Kendall, J. D. US 2513923, **1950**. (b) Lacova, M. *Chem. Papers* **1986**, *40*, 95.

(16) **Representative Procedure: DCC Coupling of Acid 7 and 1,6-Hexanediol (Scheme 4)**
A stirred solution of acid **7** (500 mg, 98 wt%, 1.90 mmol) and 1,6-hexanediol (689 mg, 5.83 mmol) in anhyd THF (5 mL) at 0 °C under Ar was treated with DCC (423 mg, 2.05 mmol). The resulting mixture was allowed to warm slowly to r.t. and stirred for 72 h. The mixture was filtered to remove precipitated DCU, diluted with CH_2Cl_2 (5 mL), and washed successively with 1 M aq $NaHCO_3$ (2 × 5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, eluting with 40–100% EtOAc in hexanes) to yield in order of elution: the diester side-product (133 mg, 0.22 mmol, 12%), hydroxy ester **12**-9 (542 mg, 1.52 mmol, 80%), and 1,6-hexanediol (181 mg, 1.53 mmol, 37% of recoverable amount).
Data for **12**-9: colorless oil. IR (neat): 3406, 2935, 1741, 1471, 1343, 1154 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.22 (1 H, dm, *J* = 7.3 Hz), 8.03 (1 H, dm, *J* = 7.3 Hz), 7.67 (1 H, td, *J* = 7.3, 1.4 Hz), 7.62 (1 H, td, *J* = 7.3, 1.4 Hz), 4.58 (2 H, s), 4.12 (2 H, t, *J* = 6.5 Hz), 3.60 (2 H, t, *J* = 6.3 Hz), 1.59–1.42 (4 H, m), 1.30–1.18 (4 H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 161.8, 152.5, 137.0, 128.4, 127.9, 125.6, 122.5, 66.8, 62.6, 58.8, 32.4, 28.2, 25.5, 25.3 ppm. HRMS (ES^+): *m/z* calcd for $C_{15}H_{20}NO_5S_2$: 358.0783; found: 358.0782. All other hydroxy sulfones in Scheme 4 were similarly characterized and gave comparable spectral signatures.

(17) **General Procedure: Ozonolysis and Intramolecular Olefination (Table 1, Method A)**
A moderate stream of ozone was bubbled through a stirred solution of **10** (250 μmol) in CH_2Cl_2–MeOH (4:1, 5 mL) at –78 °C for 10 min. The mixture was sparged with Ar for 5 min and then treated with SMe_2 (0.5 mL) and warmed to r.t. during 20 h. The solution was concentrated in vacuo and the residual crude aldehyde taken up in CH_2Cl_2 (12.5 mL). The solution of aldehyde (≤0.02 M) was added via syringe pump during 14–18 h to a stirred 0.04 M solution of DBU (95 mg, 625 μmol, 2.5 equiv) in CH_2Cl_2 (15 mL) at –78 °C (the reaction mixture was allowed to warm slowly to r.t. during the latter half of the addition). After this time, the resulting solution was shaken with sat. aq NH_4Cl (10 mL) and the layers separated. The aqueous phase was extracted with

CH_2Cl_2 (2 × 5 mL) and the combined organic phases washed with brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the residue was effected by column chromatography (SiO_2, eluting with 10–15% EtOAc in hexanes).

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(19) **Data for (*Z*)-Lactones 2 (Table 1)**
(*Z*)-**2**-12 (n = 7): colorless oil. IR (neat): 2920, 2850, 1734, 1717, 1700, 1457 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.32 (1 H, dt, *J* = 11.7, 8.9 Hz), 5.76 (1 H, dt, *J* = 11.7, 0.9 Hz), 4.23–4.19 (2 H, m), 2.47 (2 H, q, *J* = 7.9 Hz), 1.89–1.80 (2 H, m), 1.51–1.30 (10 H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.6, 147.7, 121.8, 66.4, 26.7, 26.3, 25.7, 25.5, 24.8, 24.7, 22.3 ppm. HRMS (EI^+): *m/z* calcd for $C_{11}H_{18}O_2$: 182.1307; found: 182.1298.
(*Z*)-**2**-13 (n = 8): colorless oil. IR (neat): 2926, 2855, 1716, 1653, 1458, 1153 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.15 (1 H, dt, *J* = 11.7, 8.5 Hz), 5.78 (1 H, dm, *J* = 11.8 Hz), 4.27–4.22 (2 H, m), 2.53 (2 H, qm, *J* = 7.6 Hz), 1.73–1.65 (2 H, m), 1.55–1.32 (12 H, m) ppm. ^{13}C (100 MHz, $CDCl_3$): δ = 167.7, 147.0, 121.7, 65.4, 28.0, 27.3, 27.2 (2 C), 26.5, 26.3, 25.0, 24.8 ppm. HRMS (CI^+): *m/z* calcd for $C_{12}H_{21}O_2$: 197.1542; found: 197.1536.
(*Z*)-**2**-15 (n = 10): colorless oil. IR (neat): 2928, 2857, 1720, 1643, 1459, 1173 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.13 (1 H, dt, *J* = 11.7, 8.0 Hz), 5.78 (1 H, dt, *J* = 11.7, 1.4 Hz), 4.26–4.21 (2 H, m), 2.58 (2 H, qd, *J* = 7.9, 1.4 Hz), 1.73–1.61 (2 H, m), 1.60–1.20 (18 H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 148.2, 121.1, 64.6, 28.6, 28.4, 27.6, 27.0, 26.8, 26.63, 26.57, 26.2, 26.1, 25.2 ppm. HRMS (EI^+): *m/z* calcd for $C_{14}H_{24}O_2$: 224.1776; found: 224.1769.
(*Z*)-**2**-19 ('n = 14'): colorless oil/waxy solid. IR (neat): 2927, 2851, 1702, 1655, 1473, 1108 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.14 (1 H, dt, *J* = 11.6, 7.9 Hz), 5.77 (1 H, dm, *J* = 11.6 Hz), 4.17 (2 H, t, *J* = 5.9 Hz), 3.48–3.36 (4 H, m), 2.54 (2 H, qm, *J* = 7.4 Hz), 1.75–1.62 (2 H, m), 1.55–1.15 (18 H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 149.0, 120.6, 70.0, 69.8, 64.0, 29.7–28.0 (8 C), 25.7 (2 C), 25.5 ppm. HRMS (EI^+): *m/z* calcd for $C_{17}H_{30}O_3$: 282.2195; found: 282.2183. Minor *E*-lactones revealed by: δ_H = ca. 6.94 (1 H, dt, *J* = 15.6, 7.9 Hz) ppm. ^1H NMR data for **(*Z*)-2**-15 are in agreement with those previously reported: Hayashikoshi, T.; Abe, M.; Kurata T. *Sekiyu Gakkaishi* **1996**, *39,* 74.

(20) **Data for (*Z*,*Z*)-diolides 13 (Table 1)**
(*Z*,*Z*)-**13**-14 (n = 2): waxy solid. IR (neat): 2923, 1705, 1628, 1299 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.24 (2 H, dt, *J* = 11.7, 8.7 Hz), 5.81 (2 H, dm, *J* = 11.7 Hz), 4.20 (4 H, t, *J* = 5.1 Hz), 2.77 (4 H, q, *J* = 8.2 Hz), 1.87–1.79 (4 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 145.5, 122.5, 63.8, 28.2, 27.1 ppm. HRMS (CI^+): *m/z* calcd for $C_{12}H_{17}O_4$: 225.1127; found: 225.1128.
(*Z*,*Z*)-**13**-16 (n = 3): colorless oil. IR (neat): 2925, 1716, 1653, 1458, 1288 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.26 (2 H, dt, *J* = 11.7, 8.6 Hz), 5.75 (2 H, dm, *J* = 11.6 Hz), 4.20 (4 H, t, *J* = 5.6 Hz), 2.67 (4 H, qm, *J* = 7.5 Hz), 1.78–1.70 (4 H, m), 1.65–1.50 (4 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 146.3, 121.7, 64.3, 29.8, 29.2, 26.5 ppm. HRMS (EI^+): *m/z* calcd for $C_{14}H_{20}O_4$: 252.1362; found: 252.1370.
(*Z*,*Z*)-**13**-18 (n = 4): colorless oil. IR (neat): 2923, 2853, 1698, 1458 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.18 (2 H, dt, *J* = 11.6, 8.3 Hz), 5.75 (2 H, dm, *J* = 11.6 Hz), 4.19 (4 H, t, *J* = 5.8 Hz), 2.61 (4 H, q, *J* = 7.3 Hz), 1.70–1.40 (12 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 147.7, 121.2, 64.3, 29.7, 28.9, 28.7, 26.5 ppm. HRMS (EI^+): *m/z* calcd for $C_{16}H_{25}O_4$: 281.1753; found: 281.1754.
(*Z*,*Z*)-**13**-24 (n = 7): colorless solid; mp 58–60 °C. IR (KBr): 2917, 2850, 1719, 1700, 1465 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.19 (2 H, dt, *J* = 11.7, 8.0 Hz), 5.74 (2 H, dm, *J* = 11.7 Hz), 4.17 (4 H, t, *J* = 6.0 Hz), 2.54 (4 H, q, *J* = 7.2 Hz), 1.75–1.60 (6 H, m), 1.50–1.20 (18 H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.3, 148.6, 120.9, 64.4, 29.5, 29.33, 29.26, 29.1, 29.0, 26.4 ppm. HRMS (EI^+): *m/z* calcd for $C_{22}H_{36}O_4$: 364.2614; found: 364.2617. Data for (*E*,*Z*)-diolides **13**-14, **13**-16, and **13**-18, can be found in ref. 10b.

(21) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Boeckman, R. K. Jr.; Shao, P.; Mullins, J. J. *Org. Synth.* **2000**, *77*, 141.

(22) **General Procedure: Dess–Martin Oxidation and Intramolecular Olefination (Table 1, Method B)**
A solution of **12** (250 μmol) in anhyd CH_2Cl_2 (2 mL) was treated with DMP[21] (160 mg, 375 μmol) and stirred for 45 min at r.t. Mixture diluted with CH_2Cl_2 (10 mL) and washed successively with 10 wt% aq $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and then concentrated in vacuo. The residual crude aldehyde was taken up in CH_2Cl_2 (12.5 mL) and this solution (≤0.02 M) added via syringe pump during 14–18 h to a stirred 0.04 M solution of DBU (266 mg, 1.75 mmol, 7.0 equiv) in CH_2Cl_2 (45 mL) at r.t. After this time, the reaction mixture was quenched with sat. aq NH_4Cl (10 mL) and worked up and purified as indicated above for method A (ref. 17).