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An Organocatalytic Process for the Hydrolytic Cleavage of Dithianes Mediated by Imidazolium Ions: No Harsh Agents Required

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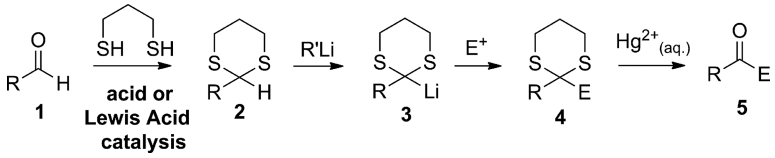
Keywords: Organocatalysis / Ionic liquids / Hydrolysis / Dithianes / Thioacetals / Aldehydes

A new, organocatalytic approach to the hydrolytic deprotection of dithianes has been developed involving a low-toxicity imidazolium-ion-based catalyst in an aqueous medium. A complimentary solvent-free method without added water and involving a sacrificial aldehyde is also reported. The catalyst does not appear to operate by a specific-acid catalysis mechanism.

Introduction

The masking of carbonyl groups as dithiane derivatives is well established as a useful and versatile tool. These groups are not only very useful for the protection of carbonyl groups against acidic/basic conditions, but also in the reversal of the reactivity of the protected carbonyl group, allowing the formation of new C–C bonds. The umpolung concept was popularised in seminal work by Corey and Seebach.[1] Thus, 1,3-dithiane-protected carbonyl compound **2** (derived from aldehyde **1**) is first converted into nucleophilic 2-lithio-1,3-dithiane species **3**. This intermediate can then react with various types of electrophiles such as alkyl halides, epoxides, and other carbonyl compounds,[2] to create a new carbon–carbon bond, e.g., in **4**. The regeneration of the carbonyl group through deprotection of the dithiane moiety to give **5** then follows (Scheme 1).

The ability to regenerate the carbonyl functionality through hydrolysis of the dithiane at a certain point during the synthesis is therefore obviously key.[3] The deprotection of these groups has generally proved difficult, particularly in cases involving sensitive substrates. Several methods using metal-based reagents have been developed.[3] These include the most widely used mercury(II)-based compounds [e.g., $HgCl_2$[4] and $Hg(ClO_4)_2$[5]] and $AgNO_3$,[6] but other metal-based compounds have also been used with varying degrees of success, including $Tl(NO_3)$,[7] $CuCl_2$,[8] $FeCl_3$,[9] $SbCl_5$,[10] $ZnBr_2$,[11] and $GaCl_3$.[12] A second commonly used method is based on the halogenative cleavage of the dithiane using either *N*-halosuccinimides [e.g., NBS (*N*-bromosuccinimide)[13,14] or NCS (*N*-chlorosuccinimide)[13,15]] or hypervalent iodine.[16] A variety of other specialised reagents have also proved effective in this deprotection reaction, including Oxone,[17] Selectfluor,[18] and Clayfen.[19] However, many of the aforementioned methods present challenges associated with toxicity or other concerns related to environmental impact, particularly many of the methods based on toxic metal ions (e.g., highly toxic mercury and thallium salts). In addition, they also generally require the use of stoichiometric amounts of the deprotection reagent, harsh reaction conditions, and/or long reaction times to regenerate the desired carbonyl compounds. Alternative, more environmentally benign methods are therefore required.



Scheme 1. Use of 1,3-dithiane-protected compounds in the formation of new C–C bonds.

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moiety in Brønsted-acid-catalysed reactions was first described by Forbes and Davis in 2002 (e.g., **6**, Figure 1).[21,22] Later, the use of protonated imidazolium ions[23] (e.g., **7**) and imidazolium ions with acidic counterions[24] (e.g., **8**) in various acid-catalysed reactions was reported. An example of the latter class of ionic liquids has been used in the deprotection of dithioacetals: Singh et al. used [bmim]HSO_4 as a reagent, at stoichiometric loadings, under microwave conditions.[25] While this potentially represents a step forward, the environmental impact of these strongly Brønsted acidic materials is currently unknown.

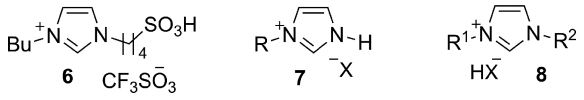


Figure 1. Classes of imidazolium-ion-based acidic ionic liquids.

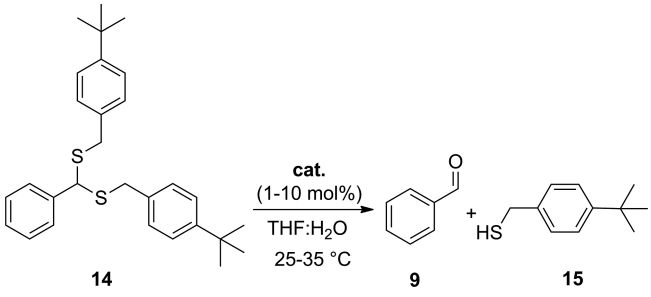
We recently reported a generation of aprotic ionic liquid catalysts that are capable of behaving as Brønsted acids in an "on-off" fashion, controlled by the use of protic additives (e.g., imidazolium ion **11**[26a] and triazolium ion **12**,[26b] Figure 2A). The optimum catalyst that emerged from this programme, i.e., **13**, could promote ambient-temperature acetalisation and thioacetalisation reactions of a range of aldehydes at catalyst loadings of 0.1–1 mol-%, and could also catalyse the reverse hydrolytic process involving acetals at low loadings.[27] More importantly, these catalysts were developed as part of our tandem strategy[26–31] to design safer chemicals (including organocatalysts and ionic liquids[31–33]) based on principles of toxicity, biodegradation, green catalyst preparation, green chemistry metrics, and performance.[34] Previous studies had shown that catalysts **11**–**13** had a low toxicity to a representative range of microorganisms (i.e., 8 bacteria and 12 fungi).[28]

We were therefore intrigued as to whether these catalysts could promote the hydrolytic deprotection of dithianes. Such a process would hold promise as a fundamentally greener alternative to existing methods.

Results and Discussion

Figure 2B shows the proposed mode of action of **13** in acetalisation reactions: the equilibrium between **13a** and **13b/13c** is driven towards the latter pair (which are the putative acid catalysts in the reaction) through the installation of electron-withdrawing substituents onto the imidazolium cation core, which further reduces delocalisation and favours nucleophilic attack by the alcohol on the heterocycle.[29] We envisaged that this electrophilic cation would also be susceptible to attack by nucleophilic thiol-based intermediates in a dithiane-hydrolysis reaction.

An initial test of this hypothesis was undertaken using imidazolium-ion-based catalysts **11** and **13** in the hydrolytic deprotection of dithioacetal **14** to give aldehyde **9** (Scheme 2, Table 1) in aqueous THF at 25 °C. Gratifyingly, imidazolium-ion-based catalyst **13** mediated the cleavage of the dithioacetal protecting group to regenerate parent aldehyde **9** in 32% yield at 1 mol-% loading (Table 1, entry 1). This result was promising, as despite the low yield, the use of the conventional strong-acid catalyst *p*TSA (*p*-



Scheme 2. Catalytic hydrolysis of dithioacetal **14**.

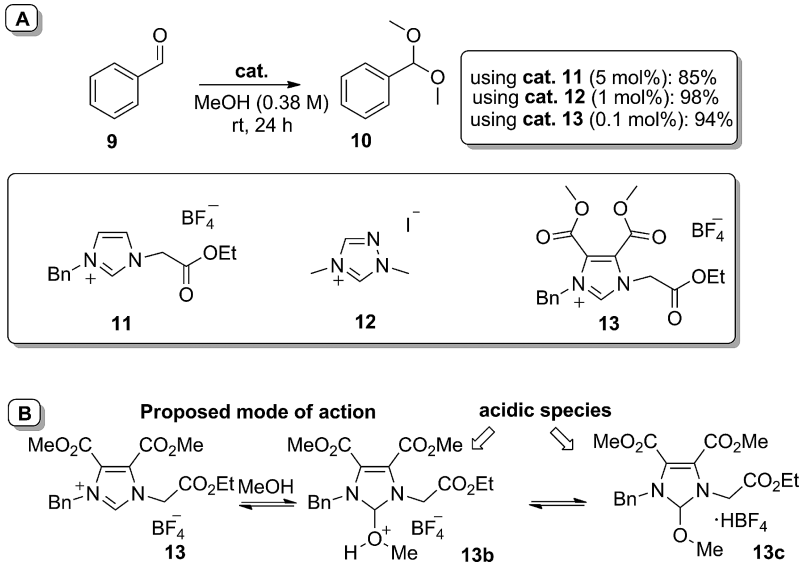


Figure 2. Catalytic imidazolium-ion-based acidic ionic liquids, and the proposed mode of action of catalyst **13**.

toluenesulfonic acid), under the same conditions, resulted in a negligible yield of the desired aldehyde product (Table 1, entry 2), and the use of H_2SO_4 (Table 1, entry 3) led to a similarly insignificant product yield.

Table 1. Catalytic hydrolysis of dithioacetal **14**: catalyst evaluation.

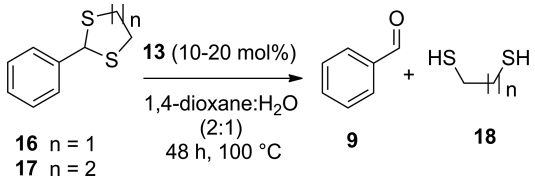
Entry	Cat.	Solvent ratio	Temp. [°C]	Time [h]	Loading [mol-%]	Yield [%][a]
1	**13**	5:1	25	24	1	32
2	*p*TSA	5:1	25	24	1	2
3	H_2SO_4	5:1	25	24	1	5
4	**11**	5:1	25	24	1	0
5	**13**	5:1	25	24	5	40
6	**13**	5:1	25	24	10	59
7	**13**	5:1	25	24	20	61
8	**13**	5:1	35	24	10	63
9	**13**	5:1	35	24	20	63
10	**13**	5:1	35	48	10	65
11	**13**	2:1	35	48	10	71
12	**13**	1:1	35	48	10	79
13	**13**	1:2	35	48	10	36
14	**13**	1:1	35	48	10 (×2)[b]	90

[a] Isolated yield after chromatography. [b] Second portion of catalyst added after 24 h.

It is clear that the presence of electron-withdrawing groups at the C-4 and C-5 positions of the heterocyclic catalytic cation is paramount, as unsubstituted catalyst **11** was found to be completely ineffective in promoting the reaction (Table 1, entry 4). Optimisation of the reaction conditions to improve the product yield was then undertaken. An incremental increase in catalyst loading from 1 to 20 mol-% was evaluated, and an increase in the amount of aldehyde generated was observed when the catalyst loading was increased from 1 to 5 mol-% (Table 1, entries 1 and 5) and again from 5 to 10 mol-% (Table 1, entries 5 and 6). It was interesting to note that doubling the catalyst loading from 10 to 20 mol-%, at both 25 °C (Table 1, entries 6 and 7) and 35 °C (Table 1, entries 8 and 9), had little effect on the product yield. The reaction time was also extended from 24 to 48 h, and a marginal increase in efficacy was observed (Table 1, entries 8 and 10). The solvent was modified next. An increase in the amount of H_2O relative to THF led to a smoother hydrolysis (Table 1, entries 10–13), and a 1:1 v/v mixture proved optimal. Since the reaction mixture was homogeneous in all cases, we would suggest that the reduced yield observed in a predominantly aqueous medium may be due to competitive degradation of the catalyst (Table 1, entry 13).

The plateau in catalytic activity observed when the catalyst loading was increased from 10 to 20 mol-% is also noteworthy (Table 1, entries 8 and 9). We questioned whether this could be due either to the catalyst system reaching equilibrium under these conditions, or to degradation of the catalyst by hydrolysis/thiolysis. We therefore tested whether the yield could be increased by adding further catalyst **13** during the reaction. Using the hitherto optimum 1:1 solvent ratio (THF/H_2O), we initially added 10 mol-% of **13** and allowed the reaction to progress for 24 h, after which time further catalyst (also 10 mol-%) was added. Under these conditions, the yield of **9** increased from 79% (Table 1, entry 12) to 90% (Table 1, entry 14).

As **13** was an effective catalyst for the hydrolysis of dithioacetal **14**, we investigated its ability to promote the cleavage of the more synthetically relevant dithiolane **16** and dithiane **17** under the optimised conditions. Initial experimentation was undertaken using dithiane **16**, using the hitherto most advantageous conditions used for the hydrolysis of **14** (i.e., using a THF/H_2O solvent mixture). We found that under these conditions the reaction proceeded to give a relatively low product yield of 54%. We therefore decided that a change of solvent may be beneficial, in order to allow for a further temperature increase to 100 °C. Therefore THF was replaced with 1,4-dioxane in a 2:1 ratio with water (Scheme 3, Table 2). We found that in this solvent mixture, catalyst **13** promoted the hydrolysis of dithiolane **16** (Table 2, entry 1) and dithiane **17** (Table 2, entry 2) to give appreciable yields of the desired aldehyde (i.e., **9**). Furthermore, the addition of two separate portions (10 mol-%) of the catalyst over 48 h, at 24 h intervals, resulted in the deprotection of these challenging thioacetal protecting groups, cleanly generating **9** in synthetically useful yields.



Scheme 3. Dithiolane/dithiane deprotection.

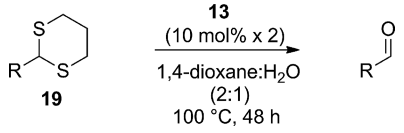
Table 2. Dithiolane/dithiane deprotection: effect of catalyst loading.

Entry	Substrate	Loading [mol-%]	Yield [%][a]
1	**16**	10	72
2	**17**	10	76
3	**16**	10 (×2)[b]	83
4	**17**	10 (×2)[b]	87

[a] Isolated yield after chromatography. [b] Second portion of catalyst added after 24 h.

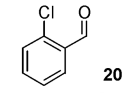
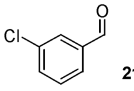
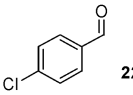
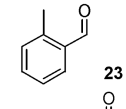
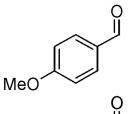
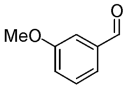
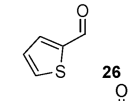
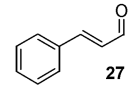
Having established an efficient procedure, we went on to evaluate the performance of **13** in the deprotection of a variety of different dithianes of general type **19** (Scheme 4, Table 3). Imidazolium salt **13** was found to catalyse the cleavage of activated (i.e., **20**–**22**, Table 3, entries 1–3), hindered (i.e., **23**, entry 4), deactivated (i.e., **24** and **25**, entries 5 and 6), heterocyclic (i.e., **26**, entry 7), and α,β-unsaturated (i.e., **27**, entry 8) aldehyde-derived dithianes to give the aldehydes in good to excellent isolated yields.

The clear superiority of **13** over strong Brønsted acids such as *p*TSA and sulfuric acid cannot be readily explained using a rationale based on the generation of transient acidic species in the presence of protic media alone. Although a full mechanistic picture has so far proved elusive (for instance, no intermediates could be detected by ^{1}H NMR



Scheme 4. Organocatalytic hydrolysis of dithianes.

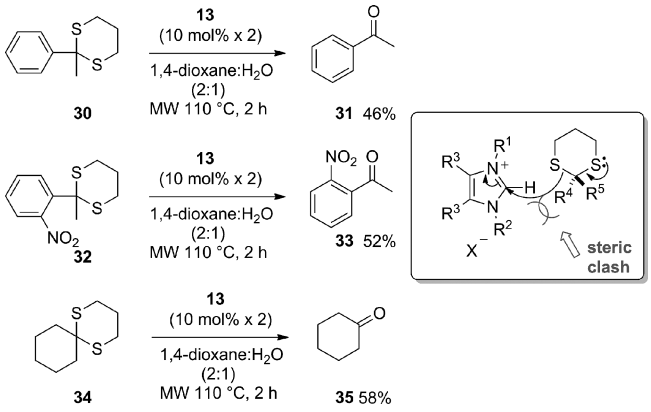
Table 3. Organocatalytic hydrolysis of dithianes: substrate scope.

Entry	Product	Yield (%)[a]
1	 **20**	78
2	 **21**	86
3	 **22**	84
4	 **23**	65
5	 **24**	76
6	 **25**	74
7	 **26**	78
8	 **27**	85

[a] Isolated yield after chromatography.

spectroscopic analysis of the reaction), at this point it seems plausible that the electrophilic catalyst may serve as a temporary trap for the thiol generated from the cleavage of the first C–S bond of the dithiane/dithioacetal to generate catalyst adduct **28** (Scheme 5). If this trapping process retards reformation of the dithiane enough for attack of solvolytic water on alkylated thioketone **28** to compete effectively, then efficient hydrolysis could occur. Presumably acid catalysis also plays a role in the regeneration of **13** from **29** (a general-acid catalysis mechanism is shown, however specific-acid catalysis through direct protonation of **29** is also possible).

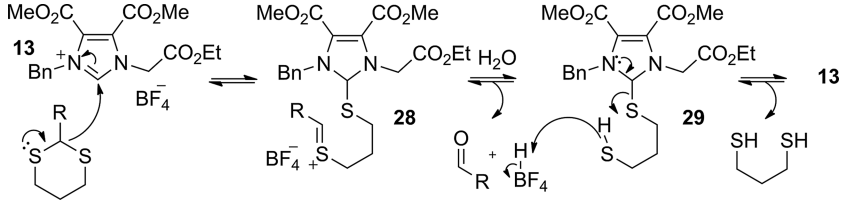
The catalytic activity of **13** in the hydrolysis of ketone-derived dithianes was also investigated. However, under the conditions described above, the more arduous task of deprotection of such ketone-derived thioacetals proved impossible. However, under the influence of microwave radiation (Scheme 6), we found that acetophenone (**31**)-derived dithiane **30** could be deprotected in 48% yield. The *o*-nitro analogue (i.e., **33**) was generated from **32** in a marginally higher yet still moderate yield, and the highest yield was observed for the regeneration of cyclohexanone (**35**) from **34**.



Scheme 6. Catalytic deprotection of ketone-derived dithianes.

The lower yields (and harsher conditions required) associated with the deprotection of these ketone-based dithianes, when compared to the aldehyde-derived analogues, supports the proposed mode of action of the catalyst in these reactions. If the rate-determining step is attack of the dithiane at the C-2 position of the imidazolium cation, the inefficient cleavage of the ketone-derived compounds may be due their greater steric bulk (Scheme 3, inset). When R^4 is H, this will allow a relatively easy addition of the thiol to the C-2 position of the heterocycle, but substitution by a methyl group (at R^4) will contribute to a more sluggish addition due to steric hindrance, leading to lower product yields due to competitive catalyst degradation over time.

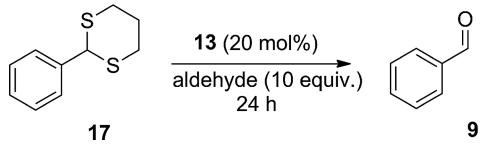
Organocatalyst **13**, though clearly much less environmentally damaging than commonly used mercury-, fluorine-, or iodine-based reagents, is of course not without its drawbacks from a green chemistry standpoint. The solvent used in the deprotection step must also be considered, especially as dioxane is classed as an "undesirable" solvent by the



Scheme 5. Proposed mode of action of catalyst **13** in the deprotection of dithianes.

pharmaceutical industry.[35] Note that the solvents used with mercury- [CH_3CN/H_2O, 4:1 v/v for $HgCl_2$,[4] and THF/H_2O, 5:1 v/v for $Hg(ClO_4)_2$[5]], fluorine- (CH_3CN for Selectfluor[18]), and iodine-based reagents (DMSO for IBX[16e]) were defined as "usable" in the same study.[35] Further optimisation of our deprotection method was required, with removal of dioxane as the solvent a priority.

Therefore, an alternative, solvent-free method was also developed using a "sacrificial" aldehyde, in which an excess of an aliphatic aldehyde − chosen because dithianes are formed more easily from aliphatic aldehydes than from aromatic aldehydes[26,27] − was added to the reaction mixture to sequester the 1,3-propane dithiol as it formed. The results of this study are summarised in Scheme 7 and Table 4.



Scheme 7. Organocatalytic deprotection of dithiane **17** under solvent-free conditions: use of a "sacrificial aldehyde".

Table 4. Dithiolane/dithiane deprotection under solvent-free conditions.

Entry	Aldehyde	Temperature [°C]	Yield [%][a]
1	propanal	45	81
2	butanal	72	80
3	pentanal	100	79

[a] Isolated yield after chromatography.

It was particularly pleasing that the reaction proceeded most efficiently in propanal at a relatively low temperature (compared to the hydrolyses outlined in Table 3) to give a synthetically useful yield of the desired aldehyde product (i.e., **9**; Table 4, entry 1). Butanal and pentanal also proved effective agents, albeit at higher temperatures (Table 4, entries 2 and 3). Only one addition of catalyst was required in these reactions. Evidently, decomposition of the catalyst under these milder, drier, conditions is less problematic. It is noteworthy that this method does not require the use of aqueous conditions, which may be useful in target-oriented synthesis applications in cases where removal of a dithiane moiety from a molecule containing functionality sensitive to aqueous acidic hydrolysis is necessary. Recovery of the excess aliphatic aldehyde is easy due to the significant difference in boiling points of the desired aromatic aldehyde, the aliphatic aldehyde, and the aliphatic-aldehyde-derived dithiane.

Conclusions

A new catalytic protocol for the synthetically useful deprotection of dithioacetal and dithiolane/dithiane-protected moieties has been developed. Aqueous and anhydrous methods have been devised, both using a low-toxicity imidazolium-ion-based organocatalyst **13**. These are new, more environmentally benign, catalytic methods by which the typically arduous cleavage of dithianes can be achieved without relying on the use of toxic, environmentally unfriendly mercury/iodine-based reagents or the use of stoichiometric amounts of reagents.

The catalytic deprotection of various dithiolane- and dithiane-protected aldehydes is possible in good to excellent yields under relatively mild conditions. The hydrolysis of ketone-based dithianes can also be promoted in the presence of **13**, albeit to a lesser degree. *p*TSA and H_2SO_4 were considerably worse than catalyst **13** as acid catalysts for this reaction. This observation strongly implies that in the presence of dithianes, **13** operates by another mechanism than conventional specific Brønsted acid catalysis.

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded with 400 and 600 MHz spectrometers. Spectra recorded in $CDCl_3$ were referenced relative to residual $CHCl_3$ (δ = 7.26 ppm), those recorded in [D_6]DMSO were referenced relative to residual DMSO (H) (δ = 2.51 ppm). Chemical shifts are reported in ppm, and coupling constants in Hertz. ^{13}C NMR spectra were recorded with the same instruments (100 and 150 MHz) with total proton decoupling. Infrared spectra were obtained using neat samples with a Perkin–Elmer Spectrum 100 FTIR spectrometer equipped with a universal ATR sampling accessory. Flash chromatography was carried out using silica gel, particle size 0.04–0.063 mm. TLC analysis was carried out on precoated $60F_{254}$ slides, which were visualised by UV irradiation, and staining with $KMnO_4$ or anisaldehyde. All aldehydes were sourced commercially, and were either distilled under vacuum (if liquid) or dissolved in CH_2Cl_2 and washed with NaOH (if solid at room temp.) before use. THF was distilled from sodium and stored under argon.

General Procedure: Hydrolysis of Dithianes (procedure involving H_2O): Compound **13** (8.9 mg, 0.024 mmol) and dithiane (0.24 mmol) were added to a round-bottomed flask (10 mL) equipped with a magnetic stirring bar. 1,4-Dioxane (5 mL) and water (2.5 mL) were added. The flask was fitted with a condenser, and the reaction mixture was heated under reflux for 24 h, after which time the solution was cooled, and further **13** (8.9 mg, 0.024 mmol) was added. The reaction mixture was heated under reflux for 24 h, and the resulting solution was concentrated in vacuo. The product was then extracted with ethyl acetate (2 × 10 mL) and water (20 mL). The organic layers were combined, dried with $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. Purification of the crude material by flash chromatography (hexane/EtOAc, 5:1) gave product **9** (22 mg, 87%) as a colourless liquid.

General Procedure: Hydrolysis of Ketone-Derived Dithianes: Catalyst **13** (17.9 mg, 0.048 mmol), ketone-derived dithiane **30** (50.0 mg, 0.24 mmol), 1,4-dioxane (2.5 mL), and water (1.25 mL) were added to a microwave reaction vial (10 mL) equipped with a magnetic stirring bar. The reaction vessel was fitted with a lid, and placed in the microwave generator under reduced pressure. The mixture was stirred for 2 h at 110 °C. Upon completion of the reaction, the solvent was removed in vacuo, and the resulting residue was purified by flash column chromatography (hexane/EtOAc, 8:1) to give product **31** (13 mg, 46%) as a colourless liquid.

General Procedure: Hydrolysis of Dithianes (anhydrous procedure): Compound **13** (37.2 mg, 0.1 mmol) was added to a reaction vessel

(10 mL) equipped with a magnetic stirrer, and the reaction vessel was put under argon. Compound **17** (98 mg, 0.5 mmol) and aliphatic aldehyde (5 mmol) were added to the reaction vessel by syringe. The reaction mixture was stirred at the required temperature for 24 h. Purification of the crude material by flash chromatography (hexane/EtOAc, 5:1) gave product **9** (43 mg, 81%) as a colourless liquid.

Supporting Information (see footnote on the first page of this article): Experimental procedures and NMR spectra.

Acknowledgments

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