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Tandem Oxidation Processes for the Preparation of Functionalized Cyclopropanes

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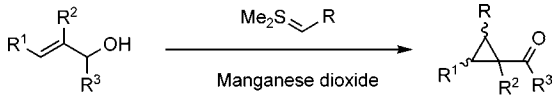
ABSTRACT



18 examples, 36-100%

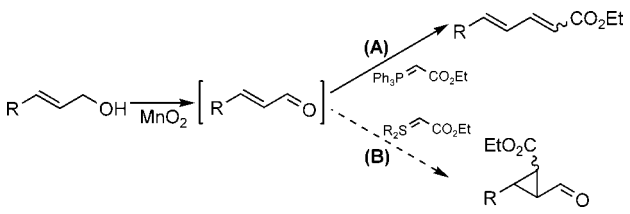
A novel manganese dioxide-mediated tandem oxidation process (TOP) has been developed which allows the direct conversion of allylic alcohols into cyclopropanes, the intermediate aldehydes being trapped in situ with a stabilized sulfur-ylide. This methodology has been applied successfully to a variety of allylic alcohols and to a formal synthesis of the simple, naturally occurring lignan, (±)-picropodophyllone.

We have had a long-standing interest in the development of manganese dioxide mediated tandem oxidation processes (TOPs) for the elaboration of alcohols.[1] These TOP methodologies offer a number of advantages to the organic chemist: they are operationally simple, the MnO_2 and its byproducts being removed by a simple filtration; they result in a reduced number of operations, giving significant time-cost benefits; they allow the use of "difficult" carbonyl intermediates (i.e., volatile, toxic, or noxious) as they are synthesized and elaborated in situ. All our previous research has concentrated on trapping intermediate carbonyl compounds via 1,2-addition, e.g., oxidation−Wittig trapping (Scheme 1A) or oxidation−imine formation,[1] and we were interested to see if the concept could be extended to 1,4-additions of α,β-unsaturated compounds generated in situ (Scheme 1B).

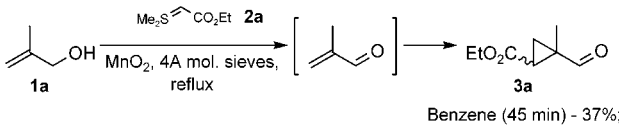
The cyclopropane moiety is an important motif in organic chemistry, found in many natural products and biologically active compounds,[2] and there are numerous methods for its synthesis.[3] One established procedure involves the 1,4-addition of a stabilized sulfur-ylide to an α,β-unsaturated carbonyl system,[3] and we hoped that chemistry of this type could be incorporated into an MnO_2-mediated TOP sequence (Scheme 1B). As shown, the allylic alcohol would be oxidized to the intermediate aldehyde which would then be trapped by a sulfur-ylide in situ, yielding the cyclopropane.

In pursuit of this strategy, we first examined the reaction of 2-methyl-2-propen-1-ol **1a** with activated MnO_2 in the presence of (carbethoxymethylene)dimethylsulfurane **2a**[3d] and powdered 4 Å molecular sieves in benzene at reflux (Scheme 2). We were delighted to observe the formation of the desired cyclopropanecarboxaldehyde **3a**[4a] in 37% yield. We rapidly established that the use of dichloromethane as

Scheme 1. MnO_2-Mediated TOPs



Scheme 2. Synthesis of Cyclopropane **3a** via TOP Methodology



Benzene (45 min) - 37%;
CH_2Cl_2 (3 h) - 71%

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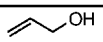
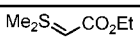
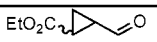
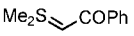
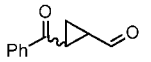
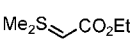
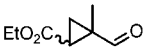
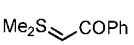
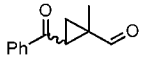
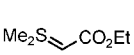
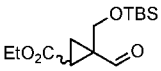
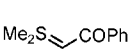
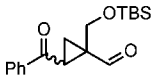
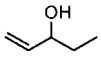
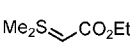
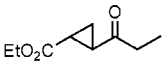
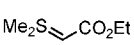
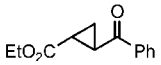
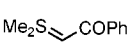
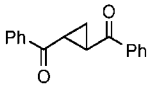
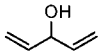
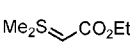
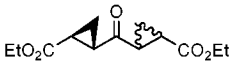
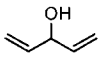
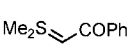
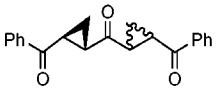
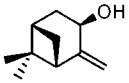
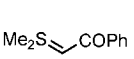
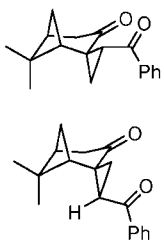
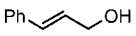
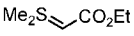
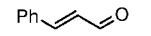
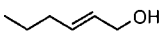
Table 1. MnO_2-Mediated TOP Methodology for the Preparation of Cyclopropanes[5,6]

Entry	Alcohol		Sulfurane		Product		Ratio (*trans*:*cis*)	Isolated Yield
i		**1b**		**2a**		**3b**[4a]	~3.0:1	36%[a]
ii		**1b**		**2b**		**3c**[4h]	~3.1:1	77%
iii		**1a**		**2a**		**3a**[4c]	~5.0:1	71%
iv		**1a**		**2b**		**3d**	~4.2:1	53%
v		**1c**		**2a**		**3e**	~3.6:1	74%
iv		**1c**		**2b**		**3f**	~2.0:1	73%
vii		**1d**		**2a**		**3g**[4d]	All *trans*	67%
viii		**1e**		**2a**		**3h**[4e]	All *trans*	100%
ix		**1e**		**2b**		**3i**[4f]	All *trans*	78%
x		**1f**		**2a**		**3j**	All *trans*	60%
xi		**1f**		**2b**		**3k**	All *trans*	69%
xii		**1g**		**2b**		**3l**	~5.0:1[b]	76%
xiii		**1h**		**2a**		**3m**	-	(quant.)[c]
xiv		**1i**		**2a**		**3n**	-	(quant.)[c]

[a] It is probable that the low yield for this example is due in part to the volatility of **3b**. [b] Of a possible four isomers, this product was isolated as a ~5.0:1 mixture of just two. We are not yet able to unambiguously assign the major isomer. [c] Based on ^{1}H NMR analysis of the unpurified reaction mixture showed only aldehyde **3m** or **3n** and ylide **2a**.

solvent gave the optimal yield, 71% as a ~5:1 *trans*/*cis* mixture of isomers.[5]

With this result in hand, we then moved on to establish the scope of the TOP-cyclopropanation methodology, with respect to the alcohol and ylide; the results are shown in Table 1.[6] Allyl alcohol **1b** also gave the desired cyclopropane **3b** (entry i), but in a low yield of 36%, presumably due in part to the volatility of the product. With (benzoylmethylene)-dimethylsulfurane **2b**,[3e] allylic alcohol **1b** gave the adduct **3c** in a much better yield of 77% (entry ii). 2-Methyl propen-1-ol **1a** also works well with ylide **2b** (entry iv). In addition, a further 2-substituted propen-1-ol **1c** proved to be a viable

(1) For examples, see: (a) Raw, S. A.; Reid, M.; Roman, E.; Taylor, R. J. K. *Synlett* **2004**, 819. (b) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Org. Biomol. Chem.* **2004**, *2*, 788. (c) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637. (d) Wei, X.; Taylor, R. J. K. *J. Org. Chem.* **2000**, *65*, 616 and references therein.

substrate, giving the desired adducts **3e**,**f** (entries v and vi). Cyclopropane **3e** (entry v) is an interesting example as it is trisubstituted, with each substituent being in a different oxidation state (i.e., alkoxy, aldehyde, and carboxylate), offering the possibility of further functionalization in a selective manner. Cyclopropane **3f** (entry vi) is similarly interesting (i.e., alkoxy, aldehyde, and ketone).

1-Substituted propen-1-ols (i.e., secondary alcohols) also gave excellent results (entries vii−xi), with good yields and complete *trans*-selectivity about the cyclopropane. Furthermore, with divinylmethanol **1f** (entries x and xi), oxidation and double-cyclopropanation occurs, giving **3j** and **3k** in 60% and 69% yield respectively, each as a mixture of isomers (~1:1 as determined by ^{1}H NMR spectroscopy).

The trends in stereochemistry seen with 1- and 2-substituted propen-1-ols are consistent with the reaction mechanism proposed by Curley and DeLuca involving equilibration of initial adducts.[4c] With 1-substituted propen-1-ols (entries vii−xi), the increased size of the substituent in the intermediate (ketone vs aldehyde) results in an equilibrium giving solely the *trans*-cyclopropane products. A more detailed analysis of the stereochemistry of these processes will be presented in a full paper.

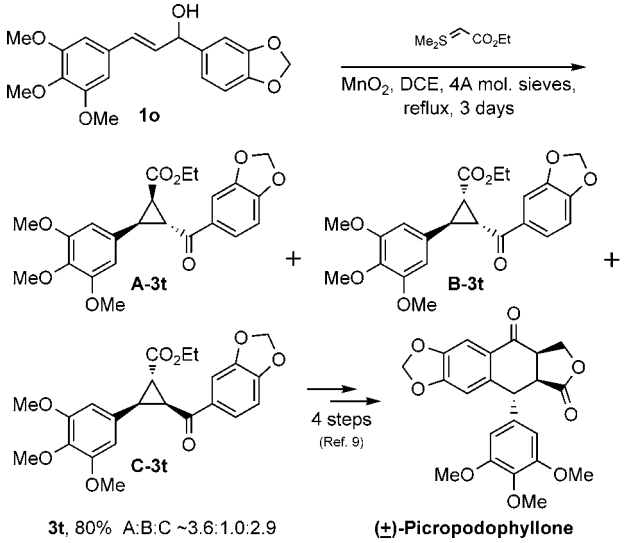
The more complex (−)-*trans*-pinocarveol **1g** also worked very well in this methodology, giving the spirocyclopropane **3l** in 76% yield (entry xii). Of the four possible isomers, this product was isolated as a ~5.0:1 mixture of just two (shown in Table 1). Models suggest these are most likely those with the benzoyl unit *cis* to the ketone, due to steric interactions in the cyclopropanation "enolate" intermediate.

We also investigated the use of 3-substituted 2-propen-1-ols (entries xiii−xiv). Unfortunately, under the current conditions, no cyclopropanation was observed with **1h** and **1i**, despite complete oxidation occurring. We are investigating the use of more reactive sulfur-ylides to allow the use of substrates such as **1h**,**i** in TOP cyclopropanations.

Next, we went on to explore the use of polysubstituted 2-propen-1-ols which, on oxidation, give chalcones which are known to be good substrates for cyclopropanation with **2a**.[7] The results are summarized in Table 2.[8] The results for these alcohols were more solvent-dependent, and each example was carried out in CH_2Cl_2, THF, and 1,2-dichloroethane (DCE), the optimum solvent being indicated in Table 2. As can be seen, in all cases the yields are good to excellent (51−100%), with electron-rich, electron-deficient, and "electron-neutral" examples being investigated. Both ylides **2a** and **2b** work well with alcohol **1j** (entries i and ii). The observed erosion of the original double bond stereochemistry is explained by the equilibration of reaction intermediates, as discussed earlier.

Finally, we examined the dihydrochalcone **1o** (Scheme 3). We were delighted to find that this was cleanly converted into cyclopropane **3t**. This result is noteworthy as **1o** is particularly electron rich, and in our experience, this slows

Scheme 3. Picropodophyllone Precursor via TOP Methodology



(2) (a) Ningsanont, N.; Black, D. S. C.; Chanpen, R.; Thebtaranonth, Y. *J. Med. Chem.* **2003**, *46*, 2397. (b) Wipf, P.; Reeves, J. T.; Balachandran, R.; Day, B. W. *J. Med. Chem.* **2002**, *45*, 1901. (c) Rugutt, J. K.; Henry, C. W.; Franzblau, S. G.; Warner, I. M. *J. Agric. Food Chem.* **1999**, *47*, 3402. (d) Han, S.-Y.; Cho, S.-H.; Kim, S.-Y.; Seo, J.-T.; Moon, S.-J.; Jhon, G.-L. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 59. (e) Barrett, A. G. M.; Doubleday, W. W.; Hamprecht, D.; Kasdorf, K.; Tustin, G. J.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1997**, 1693. (f) Bucsh, R. A.; Domagala, J. M.; Laborde, E.; Sesnie, J. C. *J. Med. Chem.* **1993**, *36*, 4139. (g) Martinez, G. R.; Walker, K. A. M.; Hirschfeld, D. R.; Maloney, P. J.; Yang, D. S.; Rosenkranz, R. P. *J. Med. Chem.* **1989**, *32*, 890.

(3) (a) For a comprehensive summary, see: Larock, R. C. *Comprehensive Organic Transformations*; VCH: New York, 1989; Chapter 4, p 71. (b) Helquist, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, Chapter 4.6, p 951. (c) Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424. (d) Payne, G. B. *J. Org. Chem.* **1967**, *32*, 3351. (e) Quintana, J.; Torres, M.; Serratosa, F. *Tetrahedron* **1973**, *29*, 2065.

(4) **General Procedure.** To a solution of monosubstituted 2-propen-1-ol in CH_2Cl_2 were added powdered 4 Å molecular sieves (1.0 g/mmol), (carbethoxymethylene)dimethylsulfurane (1.2 equiv), and activated MnO_2 (10.0 equiv). The mixture was heated to reflux and stirred until complete reaction was observed by TLC. The mixture was then filtered through Celite and the residue washed with CH_2Cl_2. Concentration of the combined organics in vacuo followed by flash column chromatography on silica gave the desired product. For more specific procedures, see the Supporting Information.

(5) All known compounds gave satisfactory data (see ref 4); all novel compounds were fully characterized by spectroscopic methods and HRMS.

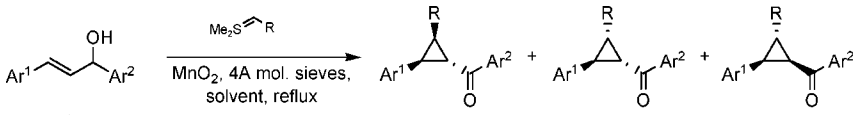
(6) (a) Boland, W.; Niedermeyer, U. *Synthesis* **1987**, 28. (b) Wu, P.-L.: Wang, W.-S. *J. Org. Chem.* **1994**, *59*, 622. (c) Curley, R. W., Jr.; DeLuca, H. F. *J. Org. Chem.* **1984**, *49*, 1944. (d) Hammerschmidt, F.; Zbiral, E. *Liebigs Ann. Chem.* **1977**, 1026. (e) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H. *J. Org. Chem.* **1982**, *47*, 4059. (f) Duhamel, P.; Poirier, J.-M.; Hennequin, L. *Tetrahedron Lett.* **1984**, *25*, 1471. (g) Aggarwal, V. K.; Smith, H. W.; Hynd, G.; Jones, R. V. H.; Fieldhouse, R.; Spey, S. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3267. For the methyl ester analogue: Adams, J.; Hoffman, L., Jr.; Trost, B. M. *J. Org. Chem.* **1970**, *35*, 1600. (h) Matano, Y. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2703 (i) Rai, K. M. L.; Anjanamurthy, C.; Radhakrisan, P. M. *Synth. Commun.* **1990**, *9*, 1273.

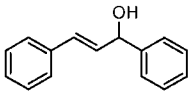
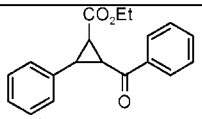
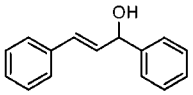
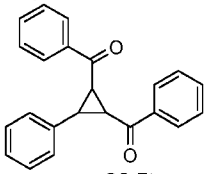
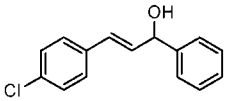
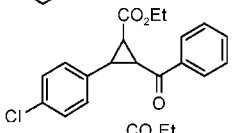
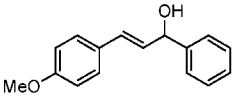
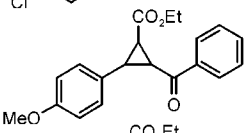
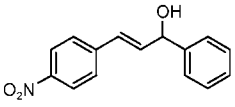
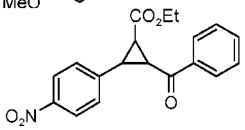
(7) For examples, see; Hantawong, K.; Murphy, W. S. *J. Chem. Res., Miniprint* **1988**, 2520 (b) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1029.

(8) **General Procedure.** To a solution of polysubstituted 2-propen-1-ol in the solvent of choice were added powdered 4 Å molecular sieves (1.0 g/mmol), (carbethoxymethylene)dimethylsulfurane (1.2−2.0 equiv), and MnO_2 (10.0 equiv). The mixture was heated to reflux and stirred until complete reaction was observed by TLC. The mixture was then filtered through Celite and the residue washed with solvent. Concentration in vacuo followed by flash column chromatography on silica gave the desired product. For more specific procedures, see the Supporting Information.

(9) Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 271.

Table 2. Polysubstituted 2-Propen-1-ols in MnO_2-Mediated TOP Cyclopropanation[6,8]



Entry	Alcohol		Ylide	Product		Solvent	Ratio (A:B:C)	Yield
i		**1j**	**2a**		**3o**[4g]	THF	5.0:1.0:3.0	70%
ii		**1k**	**2b**		**3p**[4b]	THF	In this case, A and C are enantiomers: A/C:B 2.6:1	75%
iii		**1l**	**2a**		**3q**	CH_2Cl_2	3.9:1.0:2.8	80%
iv		**1m**	**2a**		**3r**[4i]	CH_2Cl_2	4.5:1.0:2.8	51%
v		**1n**	**2a**		**3s**	CH_2Cl_2	4.0:1.0:1.6	90%

oxidation by MnO_2. Moreover, cyclopropane **3t** was utilized by Murphy and Wattanasin as a late-stage intermediate in their synthesis of (±)-picropodophyllone[9] which, along with related lignan lactones, is of interest as a cancer chemotherapeutic agent. This sequence therefore represents a formal synthesis of this simple natural product.

In conclusion, we have developed a manganese dioxide mediated tandem-oxidation process which allows the formation of functionalized cyclopropanes **3** in one step from the corresponding allylic alcohols **1**. This represents the first example of a MnO_2-mediated TOP methodology exploiting 1,4-addition to trap the intermediate carbonyl species and has been applied to a wide range of substrates. We are currently investigating the use of alternative sulfur-ylides in MnO_2-mediated TOP cyclopropanations. We also plan to apply these methodologies to target-led synthesis.

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Supporting Information Available: Experimental procedures and data for compounds not previously described in the literature (**3d**−**f**,**j**−**l**,**q**,**s**). This material is available free of charge via the Internet at http://pubs.acs.org.

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