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Microwave-Assisted Synthesis of Substituted Tetrahydropyrans Catalyzed by $ZrCl_4$ and Its Application in the Asymmetric Synthesis of *exo*- and *endo*-brevicomin

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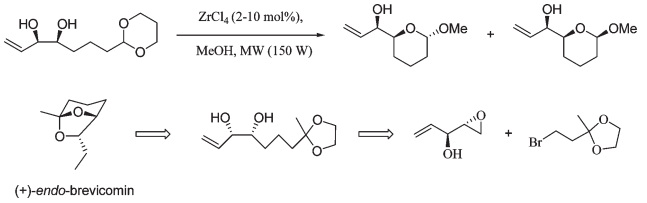
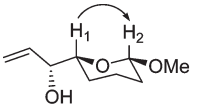


The $ZrCl_4$-catalyzed deprotection of 1,3-dioxane/dioxalane and the simultaneous formation of 6-methoxy-substituted tetrahydropyrans proceeded under microwave irradiation in good yield. This synthetic methodology was used for the asymmetric synthesis of (+)-*exo*- and (+)-*endo*-brevicomin in 55% overall yield over 4 steps.

Tetrahydropyran rings are ubiquitous in the natural product arena and many methods have been developed for their construction. Some of the most widely used methods are intramolecular epoxide opening,[1] manipulation of carbohydrates,[2] hetero-Diels−Alder cyclizations,[3,4] Prins reactions,[5] intramolecular Michael reactions,[6a] and double oxy Micheal addition of conjugated alkynoates.[6b] During a study to develop new protection/deprotection methodologies of use in total synthesis, we have recently discovered a $ZrCl_4$-catalyzed formation of δ-lactone.[7] We subsequently exploited this in an asymmetric synthesis of both enantiomers of mosquito attractant pheromones.[8] Herein, we report an extension of our investigation in this area in which we describe a microwave-assisted,[9] asymmetric synthesis of substituted tetrahydropyrans which are useful synthons for biologically important compounds.[10] In addition we have applied this methodology in a short and efficient synthesis of (+)-*exo*- and (+)-*endo*-brevicomin.

To extend our Lewis acid-catalyzed methodology we wish to study the deprotection/cyclization using diol **1** in methanol as our standard reaction development system. Diol **1** was synthesized by the ring-opening of enantiopure epoxide with the Grignard reagent derived from 2-bromoethyl-1-(1,3-dioxane).[7] The 3*R*,4*S* diol **1** was treated with $ZrCl_4$ (2−10 mol %) as the Lewis acid in MeOH under microwave irradiation, for the deprotection of the 1,3-dioxane and its subsequent cyclization to formed 6-methoxytetrahydropyrans **2** and **3** (Scheme 1, Table 1).

The epimers **2** and **3** were separable by column chromatography and the configuration of the newly formed chiral center in minor epimer **3** was assigned by ^{1}H NMR 1D- and 2D-NOESY. The anomeric proton H_2 was irradiated in a 1D-NOESY experiment and showed enhancements in the H_1 proton and also the 2D-NOESY experiments confirmed that H_1 and H_2 were correlated, suggesting that both protons are axial and hence the absolute configuration was (6*R*)-methoxytetrahydropyran **3**.



Minor epimer **3**

We attempted to optimize the reaction conditions for this transformation by varying the temperature ranges (40−80 °C) and the catalyst loading (2−10 mol %) at constant MW power (150 W) for 3 min (Table 1). The optimum temperature was found to be 50 °C with $ZrCl_4$ (5 mol %) giving an 87% yield of acetals **2** and **3** in an epimeric ratio of 75:25, respectively (entry 5). The reaction was faster under microwave irradiation compared to traditional heating at 40 °C (entry 4). Use of 2 mol % of $ZrCl_4$ was sufficient to catalyze the required transformation under similar reaction conditions, giving 76% yield in 3 min (Table 1, entry 6).

We have also screened a variety of Lewis acid catalysts for this transformation using our optimized reaction conditions with diol **1** but only $Sc(OTf)_2$ gave a good yield (65%) of desired products **2** and **3** (epimeric ratio 70:30). Other Lewis

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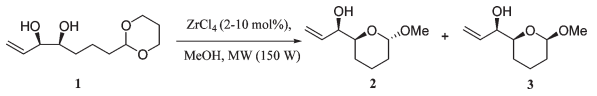
SCHEME 1



1 2 3

TABLE 1. Optimization of Microwave-Assisted Deprotection and Cyclization of 1,3-Dioxane (1) Catalyzed by $ZrCl_4$[a]

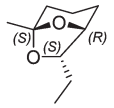
entry	catalyst loading (mol %)	temp (°C)	time (min)	isolated yield[b] (%)	epimeric ratio of (**2**:**3**)[c]
1	10	80	3	80	75:25
2	10	60	3	87	73:27
3	10	50	3	87	73:27
4	10	40	3 (2 h)[d]	84 (86)	73:27 (71:29)
5	5	50	3	87	75:25
6	2	50	3	76	73:27

[a]$ZrCl_4$ (5 mol %) and diol (0.5 mmol) were dissolved in 200 μL of methanol and irradiated under MW at 150 W. [b]Isolated yield of both epimers after purification by column chromatography. [c]Epimeric ratio was determined by ^{1}H NMR spectroscopy as well as by GC. [d]The results in parentheses refer to reactions carried out thermally at 40 °C.

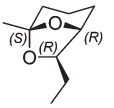
acids such as CAN, $Cu(OTf)_2$, $SnCl_2$, $Ti(O^iPr)_4$, $FeCl_3$, and $InCl_3$ did not catalyze the required transformation.

We extended our study to investigate the microwave-assisted deprotection of 1,3-dioxalane and intramolecular cyclization of (3*R*,4*S*)-diols (**4**−**8**)[7] to give the corresponding 6-methoxytetrahydropyrans **9**−**17** in good to very high yields (Table 2). 6- and 7-methyl-substituted diols (**4** and **5**) gave 84% and 76% yields of the corresponding acetals under microwave irradiation (entries 1 and 2). The best dr (80:20) was observed with diol **7** (entry 4) and this methodology was also found to be applicable for the synthesis of phenyl-substituted tetrahydropyran **16**, **17** (entry 5).

We were keen to expand this methodology by applying it in total synthesis and believed that it could be used in an asymmetric synthesis of *endo*- and *exo*-brevicomin **18** and **19**. The *exo*- and *endo*-isomers of brevicomin are constituents of volatiles from several species of bark beetles and have been shown to be necessary for their communication. (+)-*exo*-Brevicomin (**19**) is the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*.[11] (+)-*endo*-Brevicomin enhances the response of southern pine beetles, *Dendroctonus frontalis*, to the female-produced pheromone frontalin, and (−)-*endo*-brevicomin significantly reduces this response.[11e]



18; (+)-endo-brevicomin



19, (+)-exo-brevicomin

Numerous asymmetric syntheses of *endo*- and *exo*-brevicomin (**18** and **19**) have been reported but the development of a short synthetic route with overall good yield was lacking and therefore of interest.[12] Our approach involved the ring-opening of epoxide **20**, formed in 99.5% ee and 85% yield employing the Sharpless asymmetric epoxidation protocol,[7] by the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, Scheme 2. Takano's synthesis of *exo*-brevicomin in 29% overall yield and 78.5% ee required 6 steps and also started with the same epoxide **20**.[12e] Our ring-opening of epoxide **20** in the presence of CuI (10 mol %) at − 78 °C afforded *syn*-diol **21** in 80% yield. The diol **21** was treated with $ZrCl_4$ (10 mol %) in methanol under microwave irradiation to give an 86% yield of (1*R*,5*S*,7*S*)-5-methyl-7-vinyl-6,8-dioxabicyclo[3.2.1]octane (**22**) via the formation of (*S*)-1-((2*R*,6*S*)-6-methoxy-6-methyltetrahydro-2*H*-pyran-2-yl)prop-2-en-1-ol (**23**), which was also recovered in 12% yield. Acetal **23** could be quantitatively transformed into the required compound **22** upon treatment with $ZrCl_4$ in MeOH under microwave irradiation. Hydrogenation of **22** in the presence of a catalytic amount of 5% Pd/C (5 wt %) at 10 bar of pressure in an autoclave gave (+)-*endo*-brevicomin (**18**) in 95% yield and ee 98.5%. The configuration of (+)-*endo*-brevicomin was confirmed by comparing the ^{1}H, ^{13}C NMR, and optical rotation[14] with literature data.[12] We have also synthesized (−)-*endo*-brevicomin **18** in 99.3% ee using the same synthetic sequence, this time starting with the enantiomer of epoxide **20**.

We have also investigated the synthesis of (+)-*exo*-brevicomin **19**, employing our $ZrCl_4$-catalyzed methodology, Scheme 3. The epoxide **20** was converted to the *p*-nitrobenzoate **24** by using Mitsunobu reaction conditions in 80% yield. The nitrobenzoate ester **24** was hydrolyzed with K_2CO_3 to afford (2*R*,3*R*)-(+) epoxide **25** in 75% yield.[13] (+)-*exo*-Brevicomin **19** was subsequently synthesized in 99.0% ee with 65% overall yield from epoxide **25** by using the same synthetic sequence as outlined in Scheme 2. The enantiomeric purity was determined by using a chiral β-Dex GC column and the absolute configuration was determined by comparing the optical rotation[14] with literature data.[12]

In summary, we have developed a microwave-assisted $ZrCl_4$-catalyzed synthesis of 6-methoxy-substituted tetrahydropyrans in good to very high yields. We have also used this

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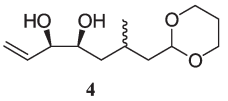
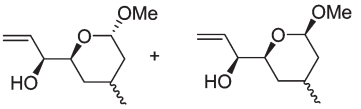
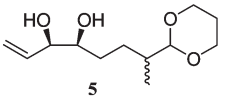
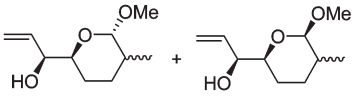
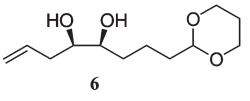
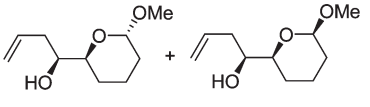
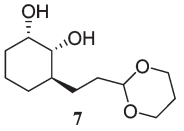
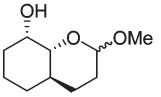
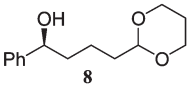
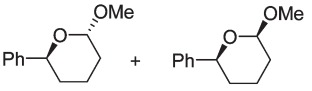
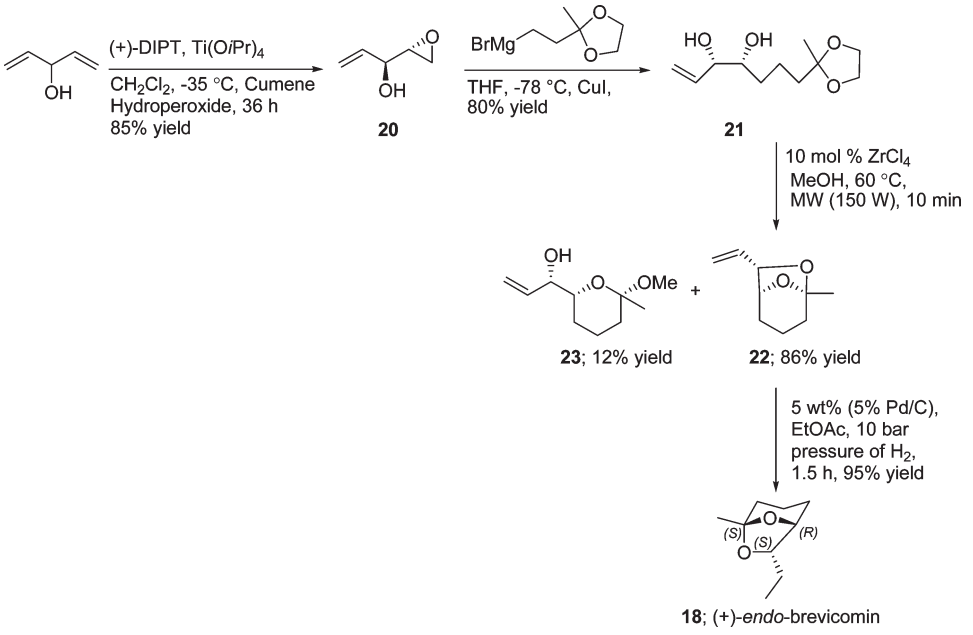
(14) Optical rotation for (+)-*endo*-brevicomin $[\alpha]^{20}_D$ +77.9 (*c* 1.2, Et_2O, 98.5% ee) [lit.[12c] $[\alpha]^{20}_D$ +78.8 (*c* 0.5, Et_2O), lit.[12e] $[\alpha]^{26}_D$ +74.6 (*c* 1.06, Et_2O)], lit.[12f] $[\alpha]^{21}_D$ +79.5 (*c* 1.18, Et_2O)], (−)-*endo*-brevicomin $[\alpha]^{20}_D$ −76.6 (*c* 1.5, Et_2O, 99.3% ee), [lit.[12c] $[\alpha]^{20}_D$ −75.9 (*c* 0.717, Et_2O), lit.[12b] $[\alpha]^{20}_D$ −76.7 (*c* 2.0, Et_2O), lit.[12f] $[\alpha]^{22}_D$ −78.9 (*c* 0.99, Et_2O)], and (+)-*exo*-brevicomin $[\alpha]^{20}_D$ + 76.3 (*c* 1.35, ether, 99.0% ee), [lit.[12a] $[\alpha]^{20}_D$ + 84.2 (*c* 2.2, Et_2O), lit.[12m] $[\alpha]^{20}_D$ + 67.9 (*c* 1.41, Et_2O), lit.[12d] $[\alpha]^{20}_D$ + 64.8 (*c* 1.25, $CHCl_3$)].

TABLE 2. $ZrCl_4$-Catalyzed Deprotection and Cyclization of Various (3*R*,4*S*)-Diols (4−8)[a]

Entry	Substrates	Products	Isolated yield[b] (%)	Diasteromeric ratio [c]
1	 **4**	 **9** **10**	84	66:33
2	 **5**	 **11** **12**	76	78:22
3	 **6**	 **13** **14**	80	66:33
4	 **7**	 **15**	90	80:20
5	 **8**	 **16** **17**	91	69:31

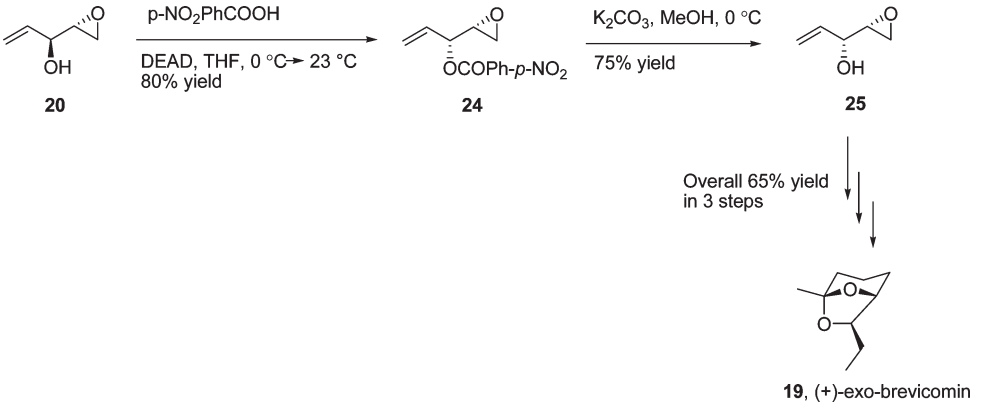
[a] $ZrCl_4$ (5 mol %) and diol (0.5 mmol) were dissolved in 200 μL of methanol and irradiated under MW (150 W) at 50 °C for 3 min. [b] Isolated yield of both epimers after purification by column chromatography. [c] The diasteromeric ratio was determined by integrating the methoxy peaks of the ^{1}H NMR spectra.

SCHEME 2



methodology for the synthesis of (+)-*endo*-brevicomin and (+)-*exo*-brevicomin, the aggregation pheromone of the western pine beetle, *Dendroctonus brevicomis*. We are currently investigating this novel methodology as the key steps in a

SCHEME 3



variety of natural product synthesis and the results of these studies will be reported in due course.

Experimental Section

Microwave Irradiation Experiments. All microwave experiments were performed with the CEM Discover Synthesizer possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in standard microwave process Pyrex vials (capacity 10 mL), using the high absorbance level. Reaction temperature was measured by the IR probe built into microwave reactor. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

General Procedure for $ZrCl_4$-Catalyzed Cyclic Acetal Formation. The diols (0.5 mmol) were dissolved in methanol (400 μL) and $ZrCl_4$ (5 mol %) was added and the solution was irradiated under MW (150 W) at 50 °C for 3 min. The title compound was purified by flash column chromatography, using pentane: EtOAc (8.5/1.5) as the eluent. The percent yield of combined epimers was given in the corresponding tables. The epimeric ratio was determined by integrating methoxy peaks of the ^{1}H NMR spectra and by GC.

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Supporting Information Available: Full experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of all intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.