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The Synthesis and Characterization of Acetamide Compounds from α-pinene and Acetonitrile through *Ritter* Reaction

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ABSTRACT: The objectives of this research were to synthesize and to characterize acetamides as α-pinene derivative compounds produced through Ritter reaction between α-pinene and acetonitrile. Turpentine oil was isolated through fractional distillation under diminished pressure of 50-100mmHg and temperature of 70-90°C, which produced 91.33% of α-pinene as the distillate. Meanwhile, the procedure of the synthesis involved dissolving acetonitrile in α-pinene, adding sulfuric acid dropwise at 6 drops per minute and stirring at room temperature, followed by extraction with diethyl eter and concentrated with N_2 gas. The compounds produced from turpentine oil isolation and synthesis through Ritter reaction is characterized by Infra-Red Spectrophotometer and Gas Chromatography-Mass Spectrometry (GC-MS). The distillate α-pinene was found to readily react with acetonitrile under the catalysis of concentrated sulfuric acid to give varieties of acetamide compounds as the products. The corresponding acetamide compounds resulted in good yields were based on its carbocation stability and rearrangement, which were N-[1-Methyl-1-(4-methyl-cyclohex-3-enyl)-ethyl]-acetamide (51.3%) as the main product and N-(2,6,6-trimethylbicyclo (3.1.1) hept-2-yl)-acetamide (4.86%) and N-(1,5-dimethyl-1-vinyl-hex-4-enyl)-acetamide (20.29%) as the by-products.

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INTRODUCTION

Indonesia is an agrarian country with rich natural resources especially in vegetation and biodiversity. In fact, it has been reported that 940 species of plants have the efficacious as drug raw materials beneficial in medicine.[1] More than 25% of the chemical compounds used in drug are estimated to be derived from plants.[2] One of the various biodiversity is pine tree, which has been widely cultivated to obtain its turpentine oil by resin distillation. Turpentine oil is one of the essential oils produced in Indonesia exported as one of the country's source of foreign exchange with the potential as diesel fuel source.[3] Turpentine oil contained approximately 70-80% of α-pinene, which is a compound that has not been used and developed in optimum based on its high value and strategic molecular enrichment. The compound can be easily obtained through fractional distillation with diminished pressure resulting in high yield of 92.02%.[4]

Due to its easiness in obtaining the material and simplicity of the isolation process, α-pinene has the potential as starting material to be further developed in the aspect of molecular structure modification to produce new beneficial compound. The structural modification of α-pinene is oriented in the formation of heterorganic compounds, which are hydrocarbon consisting of O or N atoms in various bonds, that generally have biological and physiological properties related to its potential as drug substance.

As a starting material, α-pinene can be converted to other compound due to the presence of a carbon-to-carbon double bond (alkene functional group) resulting to its reactivity through addition reaction. In general, it involves the addition of heteroatom group containing O or N atoms across the double bond of α-pinene to obtain the target molecule. The desired addition reaction is *Ritter* reaction, a chemical reaction that transforms nitrile into *N*-alkyl amide. The formation of *N*-alkyl amide proceeds through carbocation intermediate formation due to the presence of bicyclic skeletal structure of α-pinene allowing carbocation rearrangement to occur. This typically leads to the opening of four-membered ring in α-pinene so as heteroatom

substituent can be attached to carbon in various positions in the structure. Therefore, the majority (dominant) product generated through *Ritter* reaction is the compound with the heteroatom positioned at the most stable hydrocarbon intermediate.

In 1995, Dragan[5] had conducted *Ritter* reaction between tert-butyl alcohol and acrylonitrile in the presence of sulfuric acid as catalyst with excess anhydrous acetic acid to yield *N*-tert-butylacyrilamide. Secondary amide can be formed through *Ritter* reaction between 4-methyl-5,6-dihydropyran and 4-methylentetrahydropyran with MeCN, C_2H_5CN and CH_2=CHCN with H_2SO_4 as a catalyst.[6] Meanwhile, *Ritter* reaction was also further developed by Seeger and Engel[7] in synthesizing dihydroisoquinoline from tertiary alcohol and nitrile through an intermediate of amide. Parris[8] produced *N*-benzilacrylamide through *Ritter* reaction from benzyl alcohol and acrylonitrile with concentrated sulfuric acid as catalyst.

The present paper is concerned with some new contributions on the sulfuric acid catalyzed Ritter reaction between α-pinene and acetonitrile to obtain various acetamide compounds as α-pinene derivatives product, corresponding to its potential as new drug substances. The research was initiated with isolating α-pinene from turpentine oil through fractional distillation under diminished pressure, followed by synthesis of acetamide compounds through Ritter reaction between α-pinene and acetonitrile which is then characterized using Fourier Transform-Infrared (FT-IR) Spectroscopy and Gas Chromatography-Mass Spectrometry (GC-MS).

METHODS AND EXPERIMENTAL DETAILS

Materials and Apparatus

Pro-analysis reagents such as diethyl eter, acetonitrile, sulfuric acid, sodium bicarbonate ($NaHCO_3$), sodium chloride (NaCl) and anhydrous sodium sulfate (Na_2SO_4) were used without further purification. The turpentine oil was obtained from *Perhutani Trenggalek* in East Java, Indonesia.

Methods

Experimental procedures for α-pinene isolation from turpentine oil. The isolation of α-pinene from turpentine oil was performed by drying 250 mL of turpentine oil with 3 grams of anhydrous Na_2SO_4 followed by the process of fractional distillation under diminished pressure (50-100 mmHg) at approximately 70-90°C. The fractional distillation was carried out using vigreux 60 cm column and continued until the final drop of distillate. The fractional distillates obtained were then measured its density using piknometer, refractive index using refractometer, and characterized using FT-IR Spectroscopy and GC-MS.

Experimental procedures for the synthesis of acetamide compounds from α-pinene through Ritter reaction. The synthesis procedures were initiated by adding 5.2 mL acetonitrile into 16.3 mL α-pinene in a conical flask. The concentrated (98%) 21.3 mL sulfuric acid was reacted to the mixture dropwise at 6 drops per minute and then left to stir at room temperature for 5 hours. Once the reaction has gone to completion, the reaction mixture was poured onto some ice water while transferred to a separatory funnel and extracted with diethyl eter. The desired organic phase was neutralized with saturated $NaHCO_3$ and NaCl. After another extraction, the diethyl eter phase (solution) was then collected, dried with anhydrous Na_2SO_4, filtrated, and concentrated with N_2 gas. The result was analyzed with IR Spectroscopy and GC-MS.

The GC-MS analysis throughout the research was performed using Rtx-Wax column that contained polar polyethylene as stationary phase, helium as the carrier gas with flow rate of 1.5 mL/minute. Meanwhile the FT-IR spectrometry analysis was carried out using single beam optical system and KBR pellet as the sample medium.

RESULTS AND DISCUSSION

Isolation of α-pinene from Turpentine Oil through Fractional Distillation under Diminished Pressure

The turpentine oil obtained from *Perhutani Trenggalek* was analyzed using GC-MS before and after the process of fractional distillation to view whether greater percentage of α-pinene was gained. The results of physical properties and GC-MS analysis of turpentine oil and α-pinene are summarized in the Table 1.

Table 1. Fractional Distillate and Turpentine Oil Data

Physical Properties	Before Distillation	After Distillation	Standard α-pinene (INS)
Appearance	Yellow and clear	Colorless and clear	Clear Liquid
Refractive Index	1.473	1.472	1.464 – 1.478
Density	0.87 g/mL	0.91 g/mL	0.865 g/mL
α-pinene Percentage (GC-MS)	81.17%	91.33%	-

Fractional distillation under diminished pressure yielded in clear and colorless 83.42% of α-pinene as the distillate. Generally, isolating α-pinene through fractional distillation under diminished pressure gives product in high amount of α-pinene approximately 92.5 % from turpentine oil in Magelang's *Pinus merkusi*,[9] 80.46% and 93% from turpentine oil in Semarang's trade market and Center Java's *KPE Perhutani* respectively.[10]

The result of mass spectrum in GC-MS analysis showed the highest peak and similar pattern of fragmentation (m/z 50, 53, 65, 77, 93, 105, 121, and 136) both in turpentine oil and distillate at retention time of 3.3 minute, indicating that the component contained in both compounds is α-pinene with increased amount from 81.17% to 91.33%. This can be confirmed based on the characterization with GC-MS and IR Spectroscopy. The structure of α-pinene can be predicted based on fragmentation pattern from GC-MS analysis, which is summarized in Figure 1. The suggested structure of α-pinene is also supported with IR Spectrometry analysis showing specific functional groups of α-pinene summarized in Table 2 and Figure 2.

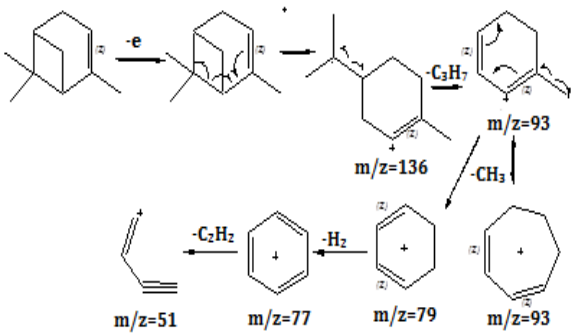

Figure 1. Fragmentation Pattern suggested for α-pinene

Table 2. Functional Groups Data on FT-IR Spectrum of Distillate

Peak	Wavenumber (cm^{-1})	Explanation of Vibration
1	3026.10	Stretching of =C-H
2	2920.03	Stretching of C-H in $-CH_3$ and $-CH_2$-
3	1656.74	Stretching of C=C
4	1446.51	Bending of $-CH_3$ and $-CH_2$-
5	1365.51	Bending of C-CH_3
6	786.90	Outward Bending of =C-H

Synthesis of Acetamide Compounds through Ritter Reaction between α-Pinene and Acetonitrile

The synthesis was performed by reacting α-pinene with acetonitrile and H_2SO_4 with molar ratio of 1:1:4,[11,12] which yielded in the formation of reddish brown viscous liquid. The area percentage data and chromatogram on GC-MS

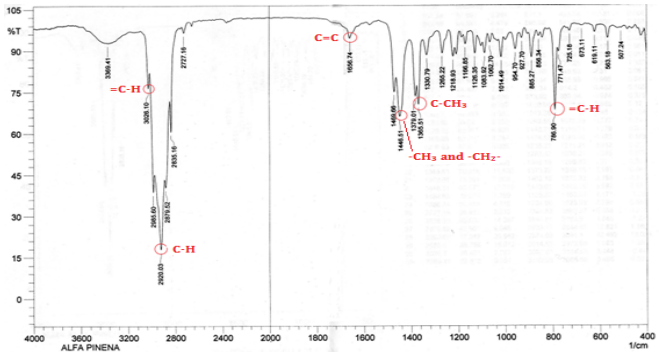

Figure 2. FT-IR Spectrum of Turpentine Oil Distillate

analysis (Table 3 and Figure 3) of the product showed the existence of 6 components in which 3 of the latter have similar molecular weight within the same range of retention times. This lead us to believe that the *Ritter* reaction was able to afford excellent yield of three compounds (peak 4, 5, 6) with different contents (Table 3), where the compound with the highest content contained the most stable carbocation to form the dominant product.

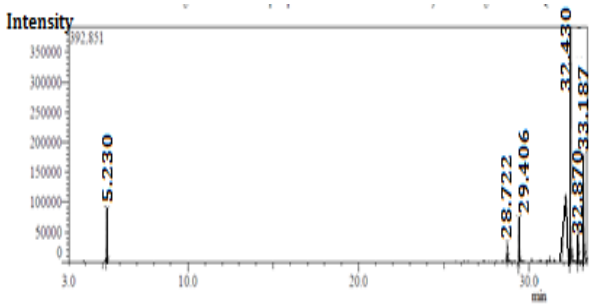

Figure 3. GC-MS chromatogram on the compounds composing the product of *Ritter* reaction.

Table 3. Retention times and % area Data of GC-MS chromatogram on the compounds composing the product of *Ritter* reaction

Peak	Retention Times (Minutes)	Area (%)
1	5.230	10.68
2	28.722	2.01
3	29.406	7.91
4	32.430	53.28
5	32.870	5.05
6	33.187	21.07

The starting material of α-pinene produced three carbocations due to rearrangement into the most stable form shown in Figure 4.

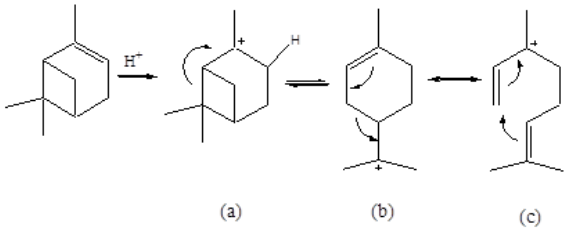

Figure 4. Carbocation formation of α-pinene

Cyclic stability is mostly associated by the strain angle between carbon-to-carbon bonds. The more strain the bond between the carbon atoms, the more tendencies for the bond to break.[13] Therefore, based on Figure 4, the order of stability from the most stable to unstable is carbocation (b), (c) and (a) respectively. Carbocation (b) has the most stable form due to its high rigidity with low steric hindrance to give strong bonds. Compare to carbocation (a), carbocation (c) has relatively higher stability due to the resonance occurring on double bond to give higher yield. Carbocation (a) has the lowest stability due to its bicyclic form as the four-ring membered resulted in a more rift bond making it easier to break.

Based on Figure 3, the dominant product (carbocation b) is the compound with the highest area percentage of 53.28% within 32.340 minutes of retention time. Meanwhile, the carbocation (c) and (a) formed byproduct compounds with area percentage of 21.07% and 5.05% within 32.870 and 33.187 minutes of retention times, respectively. The fragmentation patterns for the products are summarized in the mass spectrums shown in Figure 5.

The proposed reaction mechanisms (Figure 6), lead us into naming the compounds as N-[1-methyl-1-(4-methyl-cyclohexy-3-enyl)-ethyl]-acetamide, N-(2,6,6-trimethylbicyclo (3.1.1) hept-2-yl) acetamide, N-(1,5-dimethyl-1-vinyl-hex-4-enyl)-acetamide for carbocation (b), (a), and (c), respectively.

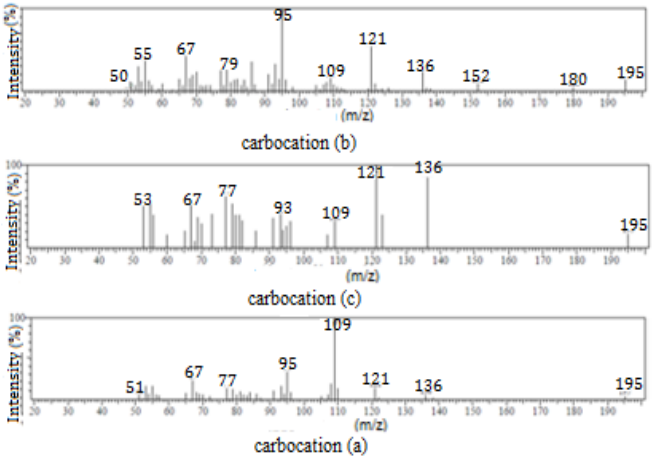

Figure 5. Mass Spectrum of the product compounds.

Throughout the *Ritter* reaction, H_2SO_4 acts as a catalyst on the protonation of double bond in the α-pinene to form carbocation as an electrophilic. As a bicyclic, α-pinene consisted of cyclobutane and cyclohexene that induced instability of the structure, which allows the opening of ring in cyclobutane to occur, resulting in the formation of two other by-products through carbocation rearrangement. The reaction then proceeds by the electrophilic addition of carbocation to the nitrile due to its lone pair existence. Nitrogen is an electronegative atom with lone pair that can act as a strong nucleophile within the acetonitrile molecule system, so as to form a strong bond between carbon and nitrogen. The addition then generate nitrilium ion to be hydrolyzed by HSO_4^- ion from the H_2SO_4 solution to the

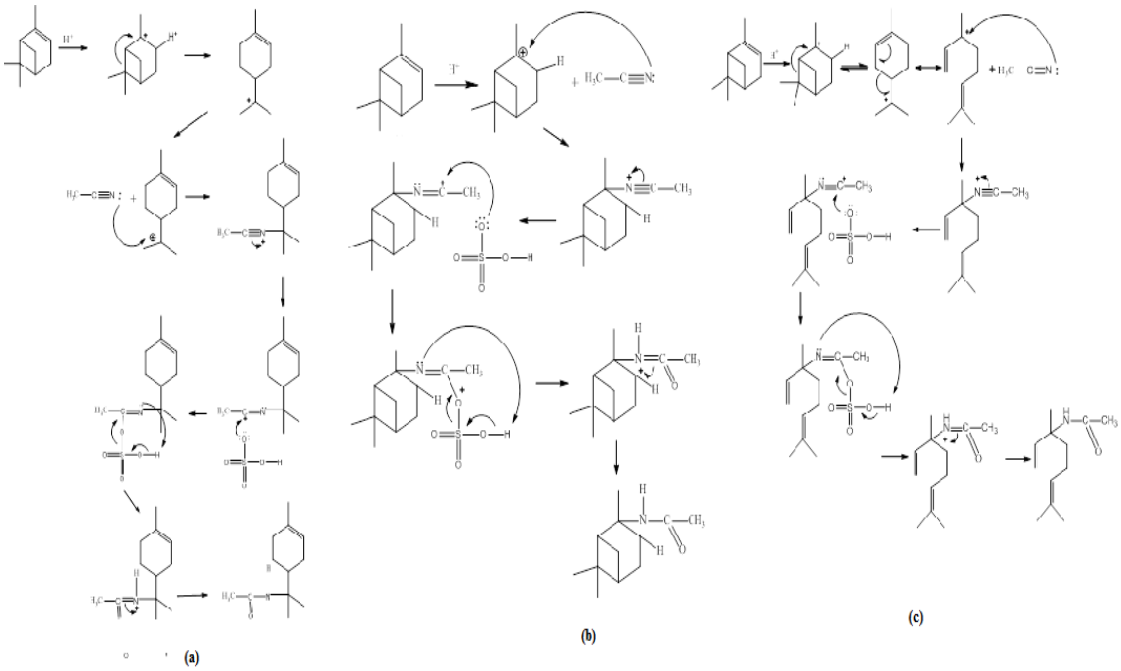

Figure 6. Proposed reaction mechanisms in the formation of N-[1-methyl-1-(4-methyl-cyclohexy-3-enyl)-ethyl]-acetamide (a), N-(2,6,6-trimethylbicyclo (3.1.1) hept-2-yl) acetamide (b), N-(1,5-Dimethyl-1-vinyl-hex-4-enyl)-acetamide (c).

desired amide. The determination of mechanism of *Ritter* reaction and structure formed as the products can be further supported by the characterization of FT-IR spectrum, summarized in Figure 7 and Table 4. A specific functional group of secondary amides can be seen in the FT-IR spectrum, which is the C=O stretch vibrational band absorbing in the wavenumber of 1647.10 cm^{-1}. Other specific functional groups can also be seen such as the N-H stretch, N-H bend, and C-N vibrational bands. Therefore, the FT-IR spectrum is capable of confirming that the resulted products of *Ritter* reaction between α-pinene and acetonitrile are indeed secondary amide. If we further analyse and compare the FT-IR spectrum of the distillate and the synthesis product, as seen in Figure 8, we would be able to recognize a striking difference in the wavenumber region of 3200-3600 cm^{-1} and 1600-1700 cm^{-1}. In the FT-IR spectrum of the distillate sharp peaks (absorption) cannot be seen in both regions, but rather emerged in the FT-IR spectrum of the synthesis product. This is indicating that *Ritter* reaction proceeded in forming carbonyl group (1630-1680 cm^{-1}) and secondary amine (3100-3500 cm^{-1}), which are characteristic of secondary amide.

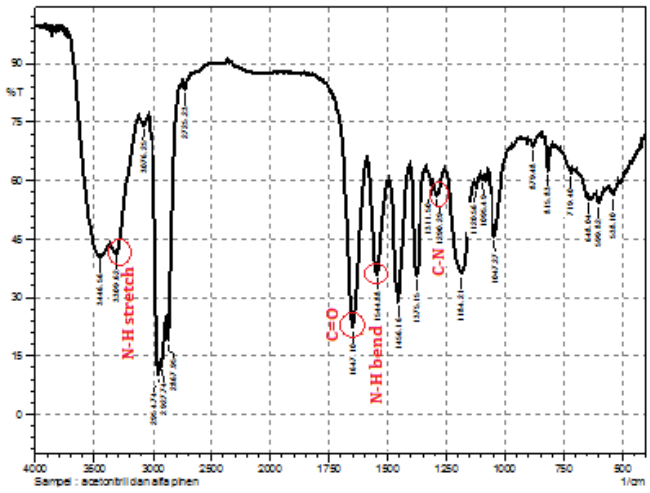

Figure 7. FT-IR spectrum of the synthesis product.

Table 4. Functional groups data of the FT-IR spectrum on the synthesis product

No.	Wavenumber	Functional Group
1	3309.62 cm^{-1}	N-H stretch
2	1647.10 cm^{-1}	C=O stretch
3	1544.88 cm^{-1}	N-H bend
4	1290.29 cm^{-1}	C-N stretch

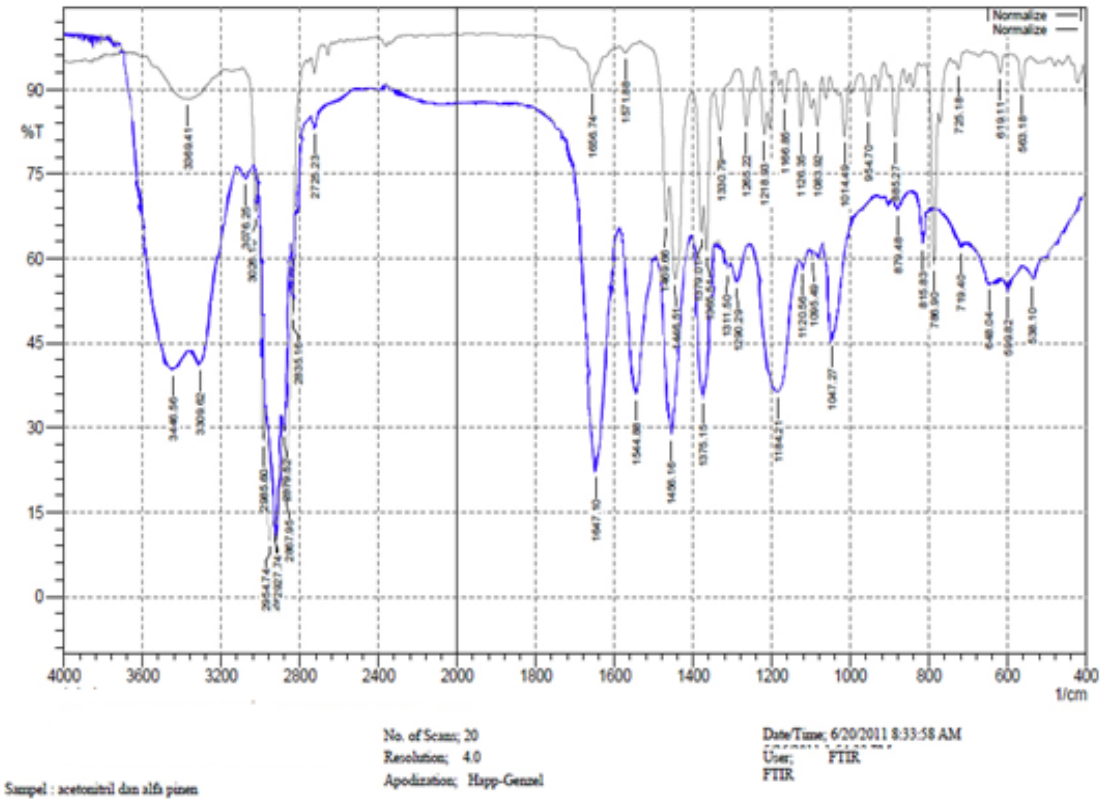

Figure 8. Comparison of FT-IR spectrum between the synthesis product (blue line) and distillate (black line).

CONCLUSION

In conclusion, we have developed further on sulfuric acid catalyzed *Ritter* reaction between α-pinene and acetonitrile, which enables the synthesis of *N*-[1-Methyl-1-(4-methyl-cyclohex-3-enyl)-ethyl]-acetamide (51.3%) as the main product and *N*-(2,6,6-trimethylbicyclo(3.1.1) hept-2-yl)-acetamide (4.86%) and *N*-(1,5-Dimethyl-1-vinyl-hex-4-enyl)-acetamide (20.29%) as the byproducts. The cheap and easy to handle α-pinene was proven to be powerful starting material for this reaction, along with the operationally simple procedures involved making it potentially useful. The development of the intramolecular version of structure modification and application of this protocol to the synthesis of natural products are potential to lead compounds for medicinal chemistry.

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