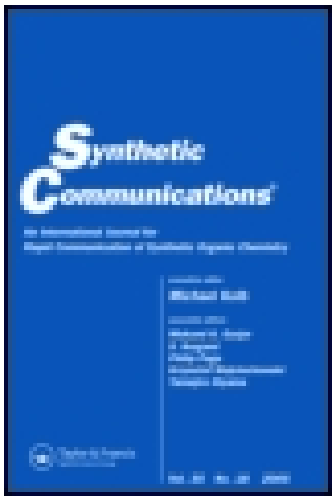

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Microwave Assisted Claisen Rearrangement: Synthesis of Naturally Occurring Trail-Resistance-overcoming Tyrosine Derivative

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MICROWAVE ASSISTED CLAISEN REARRANGEMENT: SYNTHESIS OF NATURALLY OCCURRING TRAIL-RESISTANCE-OVERCOMING TYROSINE DERIVATIVE

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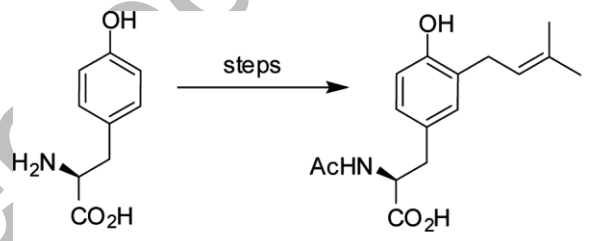
Abstract

TRAIL is a TNF family ligand that binds on the death receptors, DR4 and DR5, activating apoptotic pathways selectively in cancer cells and thus has become a promising cancer therapeutic agent. Compound **1**, isolated from *Streptomyces* sp. IFM 10937, has shown activity in overcoming TRAIL resistance in AGS cells. Synthesis of **1** has been accomplished from L-tyrosine in an overall high yielding reaction sequence.



TRAIL-resistance overcoming agent

KEYWORDS: Cancer; TRAIL; tyrosine derivative, total synthesis, olefin cross-metathesis reaction

INTRODUCTION

Cancers are genetic diseases that results from the deregulation of cell growth and cell death pathways due to genomic alterations. Apoptosis, the process of programmed cell death, is a genetically programmed biochemical process that removes unwanted cells and maintains tissue homeostasis. Tumor necrosis factor-related apoptosis inducing ligand (TRAIL), a tumor necrosis factor (TNF) family member,[1,2] activates apoptotic pathways selectively in cancer cells[3] through binding on the death receptors, DR4[4,5] and DR5[6,7]. After initiation by the death-receptor pathway, TRAIL-induced apoptosis results in activation of effector caspase-3, death-inducing signaling complex (DISC) formation and proteolytic activation of caspase-8.[8] TRAIL has emerged as an attractive antineoplastic agent due to its remarkable ability to selectively kill tumoral cells while leaving normal cells unscathed.[9] Unlike the other members of the TNF superfamily, *in vivo* administration of TRAIL has been proved to be safe.[10] However, in the case of highly malignant tumors, a reasonable numbers of cancer cells have intrinsic or acquired resistance to TRAIL-induced apoptosis.[11] Therefore, discovery of compounds that can abrogate TRAIL resistance has attracted a great deal of attention in anticancer drug discovery.

In a recent study, bioassay-guided fractionation of *Streptomyces* sp. IFM 10937, has led to the isolation of anew tyrosine derivative **1** (Figure 1).[12] Compound **1** was evaluated for their activity in overcoming TRAIL resistance in AGS (human gastric adenocarcinoma) cells. Combined treatment of 75 or 150 μM **1** and 100 ng/mL TRAIL with AGS cell lines reduced cell viability to 77 ± 7% and 67 ± 5% of control levels ($p < 0.01$), respectively, which suggested a possible synergism between the two agents.

In our ongoing efforts towards the total synthesis bioactive natural products,[13-16] we now wish to disclose the synthesis of **1**.

DISCUSSION

Synthesis of the desired compound **1** was envisaged from the olefin cross-metathesis reaction of intermediate **4**, which in turn, was to be synthesized from Claisen rearrangement of intermediate **3**. Thus, L-tyrosine **2** was converted to intermediate **3** by the operations of esterification, N-boc protection and O-allylation based on literature known procedures[17] (Scheme 1).

However, Claisen rearrangement of intermediate **3** either under thermal or microwave irradiation conditions at different temperatures, using N,N-dimethylaniline or DMF as solvents were unsuccessful. For instance, under thermal conditions reaction in N,N-dimethylaniline or DMF at reflux resulted the starting material intact whereas heating neat **3** at elevated temperatures led to the decomposition of **3**, with no desired product formation. Likewise, under microwave conditions, reaction at lower temperature (200 ^{o}C, 250 W, 1 h) in DMF resulted unchanged **3** whereas heating the reaction at higher temperature (250 ^{o}C, 250 W, 45 minutes) in N,N-dimethylaniline led to the deprotection of N-Boc group. Deprotection of N-Boc group under microwave conditions using mild base or under thermolytic conditions are well known.[18] To address the N-deprotection problem we moved on to make the N-acetyl derivative **5** which in turn was synthesized from intermediate **2** according to a literature known procedure[19] (Scheme 1). Claisen

rearrangement of intermediate **5** in N,N-dimethylaniline under microwave irradiation at 250 ^{o}C gave the desired rearranged phenol **6** in excellent yield (75%). Acetylation of intermediate **6** under standard conditions rendered **7** in a very high yield. Olefin cross-metathesis reaction between intermediate **7** and 2-methyl-2-butene, using second-generation Grubbs catalyst yielded the desired **8** in excellent yield (84%). It is noteworthy that O-prenylation of O-deallylated **5** followed by Claisen rearrangement would possibly have given access to the O-deacetylated **8**. However, such O-prenylation would have required palladium catalysed reaction between deallylated **5 w**ith commercially not available isobutyl-2-methyl-3-butene-2-ylcarbonate.[20] O-prenylation of tyrosines in proteins have recently been accomplished with prenyltransferase LynF, an enzyme from TruF family.[21,22] Finally, exposure of intermediate **8** under basic condition at room temperature ultimately produced the desired **1** in 43% overall yield from **5** (Scheme 1). All the spectral data of **1** matched with those of the previously isolated material.[12]

EXPERIMENTAL

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400 (PerkinElmer Inc. USA). IR spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR Perkin Elmer 16F PC FTIR spectrophotometer (Thermo Scientific USA). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ and CD_3OD using TMS as internal standard on a JEOL JNM-LA 500 MHz spectrometer (JEOL USA Inc.). Analytical TLC was carried out on silica gel 60 F_{254} plates (E. Merck); column chromatography was carried out on silica gel (200-400 mesh, E. Merck).

(S)-Methyl 2-acetamido-3-(3-allyl-4-hydroxyphenyl)propanoate (**6**, **$C_{15}H_{19}NO_4$**): To a microwave reaction vessel containing a solution of aryl ether **5** (0.75 g, 2.70 mmol) in N,N-dimethylaniline (4 ml). After gentle bubbling nitrogen through the solution for 1 min, the vessel was placed inside CEM Discover S-Class microwave synthesizer where it was exposed to microwaves at 250 ^oC (260 W) for 2 h. After completion of the reaction, the mixture was diluted with ethyl acetate (50 mL) and extracted with 3M hydrochloric acid (3 x 10 mL). The organic layer was washed successively with saturated sodium hydrogen carbonate (15 mL) and then brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Column chromatography purifications of the yellow oily material, eluting with ethyl acetate:hexane (1:1) yielded compound **6** as a pale yellow solid. Yield: 0.56 g, 75%; mp 91-92 ^oC; $[\alpha]_D^{25}$ +25.95 (c. 1.15, $CHCl_3$); IR (neat): 3418, 3300, 3081, 3006, 2956, 1717, 1662, 1510, 1432, 1209, 1121 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.92 (s, 3H, $NCOCH_3$), 2.96 (dd, 2H), 3.27 (m, 2H), 3.66 (s, 3H, OCH_3), 4.76 (m, 1H), 4.99-5.03 (m, 2H), 5.90 (m, 1H), 5.99 (d, 1H, *J* = 7.9 Hz, NH), 6.62 (m, 1H, aromatics), 6.72 (m, 2H, aromatics); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 23.05, 34.46, 37.05, 52.35, 53.31, 115.64, 116.07, 125.92, 127.26, 128.13, 131.04, 136.46, 153.39, 170.05, 172.29. Anal. calcd. for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.93; H, 6.94; N, 5.01.

(S)-Methyl 2-acetamido-3-(4-acetoxy-3-allylphenyl)propanoate (**7**, **$C_{17}H_{21}NO_5$**): To a solution of compound **6** (0.5 g, 1.80 mmol) in anhydrous dichloromethane (15 mL) at 0 ^oC was added triethylamine (0.75 ml, 5.41 mmol). After bring stirred for 10 minutes, acetic anhydride (0.35 ml, 3.60 mmol) was added dropwise and the reaction was stirred

for 2 h at room temperature. The mixture was added ethyl acetate (30 mL) and washed successively with saturated sodium hydrogen carbonate (15 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum to obtain compound **7** as an off-white solid. Yield: 0.57 g, 99%; mp 104 ^{o}C; $[\alpha]_D^{25}$ +56.6 (c. 1.0, $CHCl_3$); IR (neat): 3311, 3086, 2948, 1740, 1649, 1639, 1543, 1497, 1433, 1371, 1202, 1185, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.99 (s, 3H, $NCOCH_3$), 2.29 (s, 3H, $COCH_3$), 3.10 (t, 2H, *J* = 5.5 Hz), 3.25 (d, 2H, *J* = 6.7 Hz), 3.72 (s, 3H, OCH_3), 4.86 (m, 1H), 5.03-5.09 (m, 2H), 5.85 (m, 1H), 5.89 (d, 1H, *J* = 7.9 Hz, NH), 6.96 (m, 3H, aromatics); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 23.18, 29.71, 34.45, 37.16, 52.38, 53.06, 116.47, 122.47, 128.18, 131.23, 132.03, 133.70, 135.70, 148.01, 169.35, 169.61, 171.94. Anal. calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.90; H, 6.68; N, 4.32.

(S)-Methyl 2-acetamido-3-(4-acetoxy-3-(3-methylbut-2-enyl)phenyl)propanoate (**8**, **$C_{19}H_{25}NO_5$**): To a solution of compound **7** (0.23 g, 0.72 mmol) in anhydrous dichloromethane (36 ml) was added successively 2-methyl-2-butene (4 ml) and Grubbs' second generation catalyst (0.018 g, 0.021 mmol) under nitrogen atmosphere. The solution was stirred for 24 h at room temperature and concentrated under vacuum. Column chromatography of the dark brown oily material, eluting with ethyl acetate:hexane (2:3) gave compound **8** as a light yellow solid (0.21 g, 84%). Yield: 0.21 g, 84%; mp 81-82 ^{o}C; $[\alpha]_D^{25}$ -59.7 (c. 0.22, $CHCl_3$). IR (neat): 3288, 3061, 2951, 1735, 1649, 1539, 1492, 1370, 1185, 1164 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.69 (s, 3H), 1.74 (s, 3H), 1.99 (s, 3H, $NCOCH_3$), 2.30 (s, 3H, $COCH_3$), 3.10 (m, 2H), 3.25 (d, 2H, *J* =

7.3 Hz), 3.72 (s, 3H, OCH_3), 4.87 (m, 1H), 5.29 (m, 1H), 5.92 (d, 1H, *J* = 9.7 Hz, NH), 6.93 (m, 3H, aromatics); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 17.82, 23.14, 25.77, 28.59, 29.71, 37.15, 52.31, 53.03, 121.38, 122.31, 127.76, 130.83, 133.41, 133.61, 147.96, 169.41, 169.59, 171.96. Anal. calcd. for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.63; H, 7.30; N, 3.97.

(S)-2-Acetamido-3-(4-hydroxy-3-(3-methylbut-2-enyl)phenyl)propanoic acid (**1**, **$C_{16}H_{21}NO_4$**): To a solution of compound **8** (0.16 g, 0.46 mmol) in a mixture of tetrahydrofuran, methanol and water (10 ml, in 3:1:1 ratio) was added lithium hydroxide monohydrate (0.096 g, 2.3 mmol) and the mixture was stirred for 3 h at room temperature. The solvent was evaporated and residue was diluted with chloroform (20 ml) and washed with 1M hydrochloric acid (3 ml). The organic layer was dried over anhydrous sodium sulfate, concentrated under vacuum and passed over a plug of silica, eluting with methanol:dichloromethane (0.5:9.5) to afford compound **1** as a colorless solid (0.092 g, 69%). The spectral data of **1** coincided with literature values.[12]

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

ACKNOWLEDGMENTS

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Scheme 1. Synthesis of tyrosine derivative **1**.

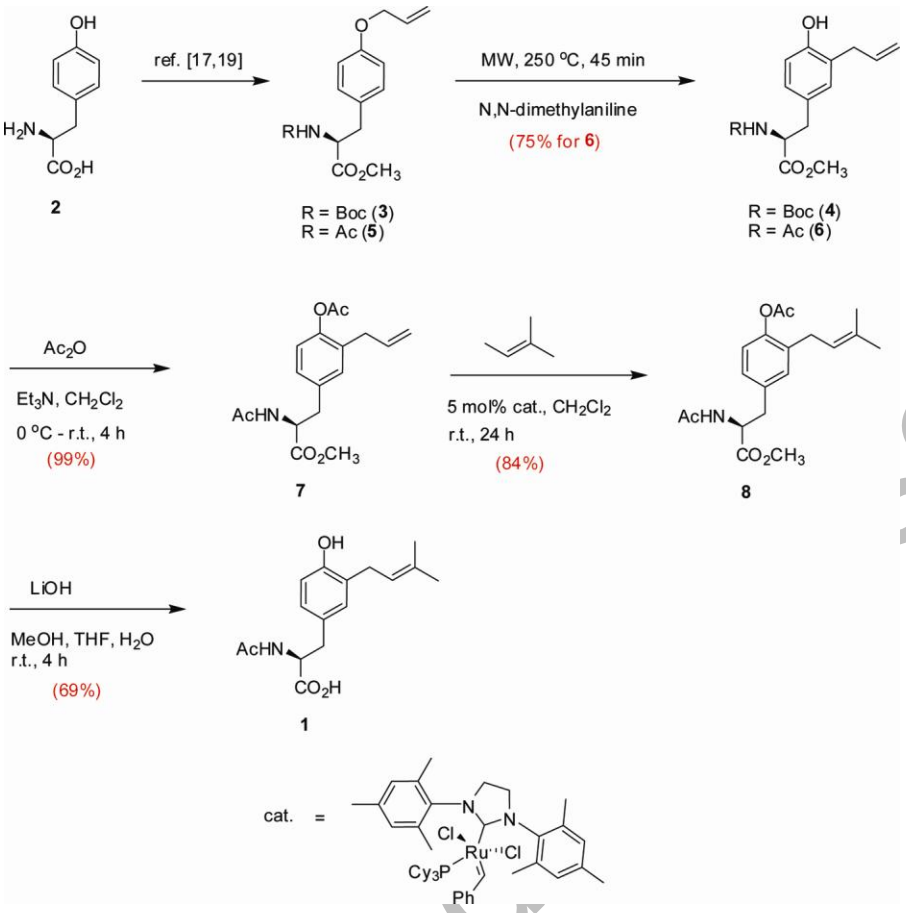
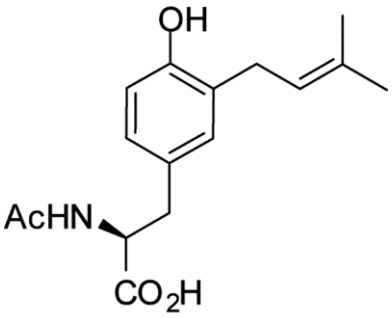


Figure 1 Chemical structure of tyrosine derivative **1**.



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