# Spectrum for <br> Enantioselective Sequential Conjugate Addition-Allylation reactions: A Concise Total Synthesis of (+)-Podophyllotoxin 

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A mixture of compound 5










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$666 E$ or






$\qquad$ 105.254


$-61.016$
$-56.236$
$\qquad$
28.314

$-76.74$
$-130.301$
119.585










Compound 2, (+)- Podophyllotoxone


Compound 2, (+)- Podophyllotoxone



Compound 1, (+)- Podophyllotoxin


Compound 1, (+)- Podophyllotoxin


Compound 1, (+)- Podophyllotoxin


## Compound 5

Data File C:\HPCHEM\4\DATA\NEW\08051950.D


Analysis Method : C:\HPCHEM\4\METHODS $\backslash Y X D 1 . M$ Last changed : 8/12/2008 4:22:55 PM (modified after loading)

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15


Area Percent Report

| Sorted By | $:$ | Signal |
| :--- | :--- | :--- |
| Multiplier | $:$ | 1.0000 |
| Dilution | $:$ | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| Peak | RetTime | Type | Width | Area | Height | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| \# | [min] |  | [min] | mAU *s | [mAU ] | \% |
| 1 | 7.420 | MM | 0.2148 | 5273.04346 | 409.10760 | 25.8408 |
| 2 | 8.755 | MM | 0.2308 | 1257.96118 | 90.84045 | 6.1647 |
| 3 | 9.577 | MM | 0.3005 | 4745.46729 | 263.19427 | 23.2554 |
| 4 | 16.946 | MM | 0.5671 | 9129.39941 | 268.30502 | 44.7391 |
| Total | $s$ : |  |  | 2.04059 e 4 | 1031.44736 |  |

Results obtained with enhanced integrator!

*** End of Report ***


Results obtained with enhanced integrator!

Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08051957$. D


WWD1 A, Wavelength $=254 \mathrm{~nm}$ (NEWI08051957.D)



| Multiplier | $:$ | Signal |
| :--- | :--- | :--- |
| Dilution | $:$ | 1.0000 |
|  |  | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | $\begin{aligned} & \text { RetTime } \\ & \text { [min] } \end{aligned}$ | Type | Width <br> [min] | ${ }_{\mathrm{mAU}}{ }^{\text {Area }}{ }^{*}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 7.350 | MM | 0.1996 | 1900.45959 | 158.66891 | 7.8269 |
| 2 | 9.485 | MM | 0.2944 | 1710.41443 | 96.84412 | 7.0442 |
| 3 | 16.522 | MM | 0.5658 | 2.06704 e 4 | 608.87732 | 85.1290 |
| Totals : |  |  |  | 2.42813 e 4 | 864.39036 |  |


(without TMEDA)

Results obtained with enhanced integrator!
*** End of Report ***

Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08051957$. D


WWD1 A, Wavelength $=254 \mathrm{~nm}$ (NEWI08051957.D)



| Multiplier | $:$ | Signal |
| :--- | :--- | :--- |
| Dilution | $:$ | 1.0000 |
|  |  | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | $\begin{aligned} & \text { RetTime } \\ & \text { [min] } \end{aligned}$ | Type | Width <br> [min] | ${ }_{\mathrm{mAU}}{ }^{\text {Area }}{ }^{*}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 7.350 | MM | 0.1996 | 1900.45959 | 158.66891 | 7.8269 |
| 2 | 9.485 | MM | 0.2944 | 1710.41443 | 96.84412 | 7.0442 |
| 3 | 16.522 | MM | 0.5658 | 2.06704 e 4 | 608.87732 | 85.1290 |
| Totals : |  |  |  | 2.42813 e 4 | 864.39036 |  |


(without TMEDA)

Results obtained with enhanced integrator!
*** End of Report ***

Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08041242$.D


$================================$
Area Perce

Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | $\begin{aligned} & \text { RetTime } \\ & {[\mathrm{min}]} \end{aligned}$ | Type | Width <br> [min] | $\mathrm{mAU}^{\text {Area }}{ }^{*}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | $\begin{gathered} \text { Area } \\ \% \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 10.943 | MM | 0.4053 | 1.16626 e 4 | 479.63235 | 50.4831 |
| 2 | 25.723 | MM | 1.0005 | 1.14394 e 4 | 190.55522 | 49.5169 |
| Total | $s$ : |  |  | 2.31020 e 4 | 670.18758 |  |



Results obtained with enhanced integrator!

*** End of Report ***

Data File C: \HPCHEM \4 \DATA $\backslash$ NEW $\backslash 08041241$. D

Injection Date : 5/7/2008 8:16:28 PM
Sample Name :
-
Acq. Operator
Acq. Method : C: \HPCHEM $\backslash 4 \backslash$ METHODS $\backslash Y X D 1 . M$
Last changed : 5/7/2008 6:38:51 PM (modified after loading)
Analysis Method : C: \HPCHEM 4 \METHODS $\backslash$ YXD1.M
Last changed : 8/7/2008 5:18:59 PM (modified after loading)
WWD1 A, Wavelength $=254 \mathrm{~nm}$ (NEW08041241.D)


Area Percent Report

|  |  | Area Perce |
| :--- | :--- | :--- |
| $=================================$ |  |  |
| Sorted By | : | Signal |
| Multiplier | : | 1.0000 |
| Dilution |  | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| $\begin{gathered} \text { Peak } \\ \# \end{gathered}$ | $\begin{aligned} & \text { RetTime } \\ & {[\mathrm{min}]} \end{aligned}$ | Type | Width <br> [min] | $\operatorname{mAU}^{\text {Area }}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | $\begin{gathered} \text { Area } \\ \frac{\%}{8} \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 10.331 | MM | 0.3596 | 686.05255 | 31.79389 | 1.9547 |
| 2 | 25.685 | MM | 0.9736 | 3.44118 e 4 | 589.06763 | 98.0453 |
| Total | $s$ : |  |  | 3.50979 e 4 | 620.86151 |  |



Results obtained with enhanced integrator!
Results with enhanced integra
*** End of Report ***

Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08041232$.D

$==================================1$
Area Percent

Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | RetTime [min] | Type | Width <br> [min] | ${ }_{\mathrm{mAU}}{ }^{\text {Area }}{ }^{\text {As }}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | $\begin{gathered} \text { Area } \\ \% \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 9.032 | MM | 0.2985 | 3.38308 e 4 | 1889.15540 | 50.3239 |
| 2 | 15.164 | MM | 0.5849 | 3.33953e4 | 951.56677 | 49.6761 |
| Total | $s$ : |  |  | 6.72261 e 4 | 2840.72217 |  |




Results obtained with enhanced integrator!


Data File C: \HPCHEM\4\DATA\NEW\08051964.D


Results obtained with enhanced integrator!

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\text { *** End of Report } * * *
$$

Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08051208$.D




Results obtained with enhanced integrator!
$\begin{aligned} &================================================ \\ & * * * \text { End of Report *** }\end{aligned}$


|  | Area Percen |  |
| :---: | :---: | :---: |
| Sorted By | : | Signal |
| Multiplier | : | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength $=254 \mathrm{~nm}$

| Peak \# | $\begin{aligned} & \text { RetTime } \\ & {[\min ]} \end{aligned}$ | Type | Width <br> [min] | $\mathrm{mAU}^{\text {Area }}{ }^{*_{s}}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | Area $\%$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 10.482 | MM | 0.3572 | 443.16467 | 20.67850 | 6.9920 |
| 2 | 21.808 | MM | 0.8173 | 5894.99805 | 120.21584 | 93.0080 |
| Total | $s$ : |  |  | 6338.16272 | 140.89434 |  |



Results obtained with enhanced integrator!

*** End of Report ***

Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08051948$. D


| Area Percen |  |  |
| :---: | :---: | :---: |
| Sorted By |  | Signal |
| Multiplier |  | 1.0000 |
| Dilution |  | 1.0000 |

Racemic sample
Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | RetTime [min] | Type | Width <br> [min] | ${ }_{\mathrm{mAU}}{ }^{\text {Area }}$ | $\begin{aligned} & \text { Height } \\ & {[m A U \quad]} \end{aligned}$ | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 11.881 | MM | 0.3683 | 1.64613 e 4 | 744.99487 | 50.4010 |
| 2 | 22.061 | MM | 0.7653 | 1.61994 e 4 | 352.77026 | 49.5990 |
| Totals : |  |  |  | $3.26607 e 4$ | 1097.76514 |  |



Results obtained with enhanced integrator


Data File C: \HPCHEM\4\DATA\NEW\08051949.D



Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | RetTime | Type | Width | Area | Height | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | [min] |  | [min] | mAU *s | [mAU | \% |
| 1 | 11.939 | MM | 0.3609 | 1713.86597 | 79.14449 | 2.7200 |
| 2 | 21.596 | MM | 0.8629 | 6.12955 e 4 | 1183.88733 | 97.2800 |
| Total | $s$ : |  |  | 6.30094 e 4 | 1263.03182 |  |



Results obtained with enhanced integrator!
$=========================================$
*** End of Report ***

## Data File C: \HPCHEM\4\DATA\NEW\08051946.D

| Injection Date | 5/31/2008 2:00:55 PM |  |
| :---: | :---: | :---: |
| Sample Name | : | Location : Vial 1 |
| Acq. Operator | : |  |
|  |  | Inj Volume : $5 \mu \mathrm{l}$ |
| Acq. Method | : C: \HPCHEM $\backslash 4 \backslash \mathrm{METHODS}$ \YXD1.M |  |
| Last changed | : 5/31/2008 12:16:26 PM |  |
|  | (modified after loading) |  |
| Analysis Method | : C: \HPCHEM $\backslash 4 \backslash$ METHODS $\backslash Y X D 1 . M$ |  |
| Last changed | : 8/7/2008 5:42:51 PM |  |

WD1 A, Wavelength $=254 \mathrm{~nm}$ (NEW08051946.D)


| Sorted By | : | Signal |
| :---: | :---: | :---: |
| Multiplier | : | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength $=254 \mathrm{~nm}$

| $\begin{gathered} \text { Peak } \\ \# \end{gathered}$ | $\begin{aligned} & \text { RetTime } \\ & \text { [min] } \end{aligned}$ | Type | Width [min] | $\mathrm{mAU}^{\text {Area }}{ }_{\mathrm{s}}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | $\begin{gathered} \text { Area } \\ \% \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 7.564 | MM | 0.2165 | 1.72536 e 4 | 1327.99866 | 49.8294 |
| 2 | 9.126 | MM | 0.2796 | $1.73717 e 4$ | 1035.63782 | 50.1706 |
| Total | $s$ : |  |  | 3.46253 e 4 | 2363.63647 |  |



Results obtained with enhanced integrator!


Data File C: \HPCHEM $\backslash 4 \backslash$ DATA $\backslash$ NEW $\backslash 08051962$. D

| Injection Date | : 6/4/2008 4:14:06 PM |  |
| :---: | :---: | :---: |
| Sample Name | : | Location : Vial 1 |
| Acq. Operator | : |  |
|  |  | Inj Volume : $5 \mu \mathrm{l}$ |
| Acq. Method | : C: \HPCHEM $\backslash 4 \backslash \mathrm{METHODS}$ \YXD1.M |  |
| Last changed | : 6/4/2008 2:57:01 PM |  |
|  | (modified after loading) |  |
| Analysis Method | : C: \HPCHEM 4 \METHODS $\backslash Y \mathrm{XD} 1 . \mathrm{M}$ |  |
| Last changed | : 8/7/2008 5:21:16 PM |  |

mAU WD1 A, Wavelength=254 nm (NEW08051962.D)
$=================================$
Area Percen

Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | RetTime [min] | Type | Width [min] | $\mathrm{mAU}^{\text {Area }}{ }_{\mathrm{*}}$ | $\begin{aligned} & \text { Height } \\ & \text { [mAU ] } \end{aligned}$ | Area \% |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 7.509 | MM | 0.2028 | 1852.20935 | 152.23366 | 5.9892 |
| 2 | 8.971 | MM | 0.2814 | 2.90734 e 4 | 1722.21594 | 94.0108 |
| Total | $s$ : |  |  | 3.09256 e 4 | 1874.44960 |  |



Results obtained with enhanced integrator!


Data File C:\HPCHEM\4\DATA\NEW\08081229.D


Results obtained with enhanced integrator!
*** End of Report ***

Data File C:\HPCHEM\4\DATA\NEW\08081230.D


|  | Area Perce |  |
| :---: | :---: | :---: |
| Sorted By | : | Signal |
| Multiplier |  | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| $\begin{gathered} \text { Peak } \\ \# \end{gathered}$ | ```RetTime [min]``` | Type | Width <br> [min] | Area | Height | $\begin{gathered} \text { Area } \\ \text { \% } \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | mAU *s | [mAU ] |  |
| 1 | 8.765 | MM | 0.2900 | 1489.49194 | 85.61259 | 3.0093 |
| 2 | 13.343 | MM | 0.5850 | $4.80075{ }^{4} 4$ | 1367.63184 | 96.9907 |
| Total | $s$ : |  |  | $4.94970{ }^{4}$ | 1453.24443 |  |



Results obtained with enhanced integrator!
*** End of Report ***

Data File C: \HPCHEM\4\DATA\NEW\08081231.D


Results obtained with enhanced integrator
*** End of Report ***

Data File C:\HPCHEM\4\DATA\NEW\08081233.D



| Area Percen |  |  |
| :---: | :---: | :---: |
| Sorted By | : | Signal |
| Multiplier |  | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| $\begin{gathered} \text { Peak } \\ \# \end{gathered}$ | $\begin{gathered} \text { RetTime } \\ \text { [min] } \end{gathered}$ | Type | width [min] | $\mathrm{mAv}^{\text {Area }}$ | $\begin{aligned} & \text { Height } \\ & \text { [mAU ] } \end{aligned}$ | $\begin{gathered} \text { Area } \\ \frac{\%}{8} \end{gathered}$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 9.262 | MM | 0.3719 | 454.12857 | 20.34921 | 1.4895 |
| 2 | 20.407 | MM | 1.1320 | 3.00347 e 4 | 442.21295 | 98.5105 |
| Total | $s$ : |  |  | 3.04889 e 4 | 462.56217 |  |



Totals : $3.04889 \mathrm{e} 4 \quad 462.56217$
Results obtained with enhanced integrator!
$\square$
*** End of Report ***

Data File C: \HPCHEM\4\DATA\NEW\08081207.D



Signal 1: VWD1 A, Wavelength $=254 \mathrm{~nm}$

| Peak\# | $\begin{aligned} & \text { RetTime } \\ & {[\text { min] }} \end{aligned}$ | Type | Width <br> [min] | Area |  | Height |  | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | mAU | *s | [mAU | ] | $\%$ |
| 1 | 8.068 | MM | 0.2584 | 4213 | 41895 | 271 | 783 | 100.0000 |
| Total | $s$ : |  |  | 4213 | 1895 | 271 | 8 |  |

Results obtained with enhanced integrator!

*** End of Report ***

Data File C:\HPCHEM\4\DATA\NEW\08081204.D


Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | $\begin{aligned} & \text { RetTime } \\ & \text { [min] } \end{aligned}$ | Type | Width [min] | $\operatorname{mAU}^{\text {Area }}{ }^{*}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | Area $\%$ |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 8.148 | MM | 0.2881 | 4305.82178 | 249.07962 | 56.6001 |
| 2 | 13.971 | MM | 0.6469 | 3301.61816 | 85.05922 | 43.3999 |
| Total | 5 : |  |  | 7607.43994 | 334.13884 |  |

Results obtained with enhanced integrator!
$========-======================================3$

Data File C: \HPCHEM\4\DATA\NEW\08081208.D


Signal 1: VWD1 A , Wavelength $=254 \mathrm{~nm}$


Results obtained with enhanced integrator!

*** End of Report ***

Data File C: \HPCHEM\4\DATA\NEW\08051975.D

|  |  |  |  |  |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |


|  | Area Percen |  |
| :---: | :---: | :---: |
| Sorted By | : | Signal |
| Multiplier |  | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm


Results obtained with enhanced integrator!


Data File C:\HPCHEM\4\DATA\NEW\08051980.D


|  | Area Perce |  |
| :---: | :---: | :---: |
| Sorted By | : | Signal |
| Multiplier | : | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| $\begin{gathered} \text { Peak } \\ \# \end{gathered}$ | $\begin{aligned} & \text { RetTime } \\ & \text { [min] } \end{aligned}$ | Type | $\begin{aligned} & \text { Width } \\ & \text { [min] } \end{aligned}$ | Area |  | Height | Area |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  |  |  |  | mAU | *S | [mAU ] |  |
| 1 | 13.278 | MM | 1.1715 | 1134 | 59558 | 16.14113 | 46.4574 |
| 2 | 18.449 | MM | 2.2870 | 1307 | 63159 | 9.52949 | 53.5426 |
| Total |  |  |  | 2442 | 22717 | 25.67062 |  |

Results obtained with enhanced integrator!

*** End of Report ***


| Area Percent Report |  |  |
| :---: | :---: | :---: |
| Sorted By | : | Signal |
| Multiplier | : | 1.0000 |
| Dilution | : | 1.0000 |

Signal 1: VWD1 A, Wavelength=254 nm

| Peak \# | $\begin{aligned} & \text { RetTime } \\ & {[\min ]} \end{aligned}$ | Type | Width <br> [min] | $\mathrm{mAU}^{\text {Area }}{ }^{*_{\mathrm{s}}}$ | $\begin{aligned} & \text { Height } \\ & {[\mathrm{mAU} \text { ] }} \end{aligned}$ | Area \% |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 13.546 | MM | 1.2788 | 1.68151 e 4 | 219.15643 | 99.6128 |
| 2 | 18.896 | MM | 1.0143 | 65.36973 | 1.07409 | 0.3872 |
| Totals : |  |  |  | 1.68805 e 4 | 220.23052 |  |

Results obtained with enhanced integrator!


