synthesis of RvE1; however, these methods are not applicable to commercial manufacture for pharmaceutical use.

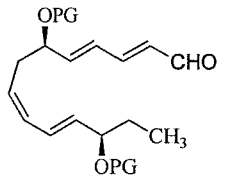
SUMMARY

[0006] The present disclosure provides various synthetic routes for the preparation of RvE1.

[0007] The synthetic routes disclosed herein, including full chemical structures of all the compounds involved, are shown in the Appendix hereinafter, **Schemes 1-19**, wherein the various starting compounds, intermediates and products referred to are herein identified by the Arabic numbers 1-48, 51-56, 59, 61, 62, 64, 65, and 68-73. RvE1 (in the form of the sodium salt thereof) is identified herein as compound 30.

[0008] Some of the compounds/intermediates synthesized are known; however, some of them are novel. The present disclosure thus provides the novel compounds 7, 8, 10, 13, 14, 15, 19, 20, 21, 23, 28, 29, 38, 39, 40, 41, 42, 47, 54, 59, 61, 65, 68, 69, 70, 71, 72, and 73, which are useful as intermediates in the syntheses disclosed herein.

[0008a] In one aspect of the present disclosure, there is provided a method for the synthesis of Resolvin E1 (RvE1) of the formula 30 starting from compounds 72 and 61, wherein PG each independently is a hydroxyl-protecting group, said method is carried out as depicted in Scheme 15 and comprises: (i) Wittig reaction of compound 72 with compound 61 in the presence of a strong base; (ii) removal of the hydroxyl-protecting groups with a deprotecting reagent to obtain compound 73; and (iii) hydrolysis of the ester group of compound 73, to obtain RvE1



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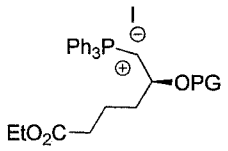

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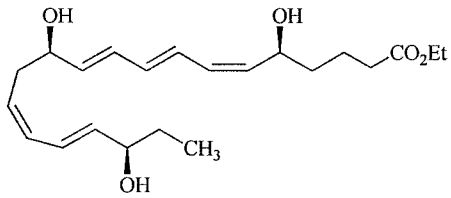

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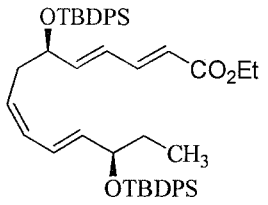
[0008b] In another aspect of the present disclosure, there is provided a method for the synthesis of Resolvin E1 (RvE1) of the formula 30 starting from compound 42, said method is carried out as depicted in Scheme 9 and comprises: (i) reduction of the ester group of compound 42 to obtain compound 48; (ii) Wittig reaction of compound 48 with compound 47 in the presence of a strong base to obtain an intermediate product: and (iii) removal of the hydroxyl-protecting groups at positions C12 and C18 of said intermediate product and

deacetylation of the protected hydroxyl group at position C5 of said intermediate product, to obtain RvE1



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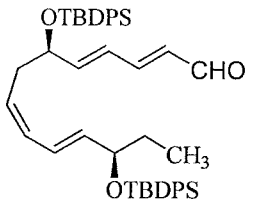

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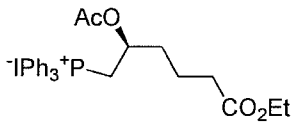

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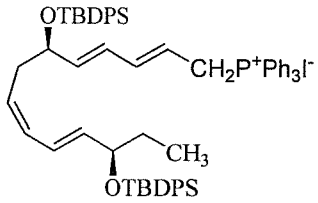
[0008c] In yet another aspect of the present disclosure, there is provided a method for the synthesis of Resolvin E1 (RvE1) of the formula 30 starting from compounds 43 and 46, said method is carried out as depicted in Scheme 11 and comprises: (i) Wittig reaction of compound 43 with compound 46 in the presence of a strong base to obtain an intermediate product; and (ii) removal of the hydroxyl-protecting groups at positions C12 and C18 of said intermediate product and deacetylation of the protected hydroxyl group at position C5 of said intermediate product, to obtain RvE1



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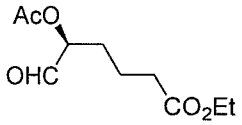

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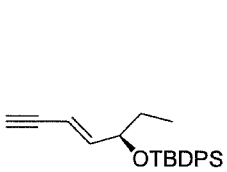
[0008d] In a further aspect of the present disclosure, there is provided a compound selected from the herein identified compounds 38, 39, 40, 41, 42, 47, 59, 61, 65, 68, 69, 70, 71, 72 and 73



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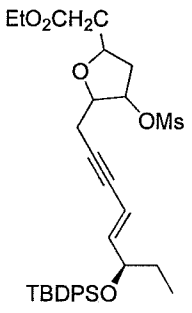

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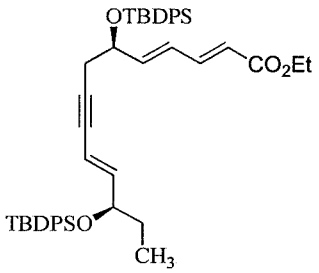

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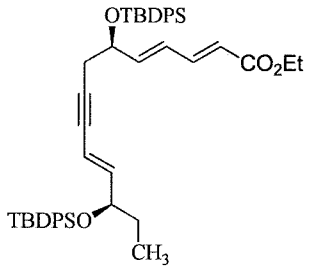

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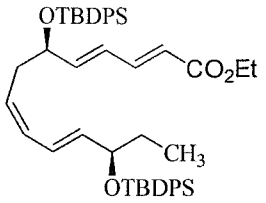

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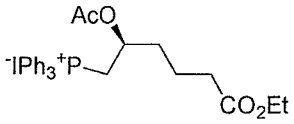

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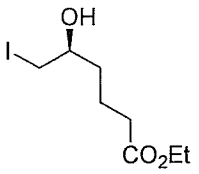

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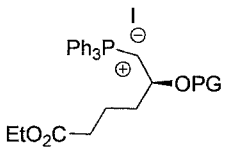

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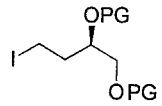

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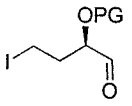

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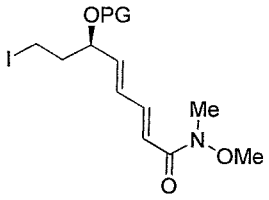

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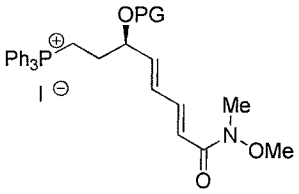

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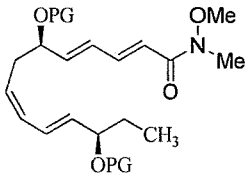

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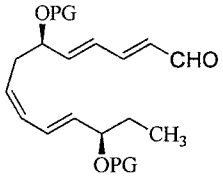

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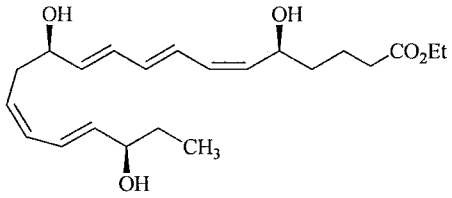

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DETAILED DESCRIPTION

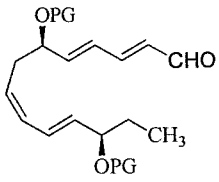
[0009] In one aspect, the present invention provides methods, i.e., procedures, for total chemical synthesis of RvE1 (compound 30).

[0010] In one particular such aspect, the invention provides a method for the synthesis of RvE1 starting from compound 28, said method is carried out as depicted in **Scheme 1** and comprises: (i) selective removal of the **TBDPS** protecting groups at positions C12 and C18 of compound 28 and reduction of the triple bond at positions 6-7 to an olefinic bond, thus resulting in compound 29; and (ii) deacetylation of the protected hydroxyl group at position C5 of compound 29, to obtain RvE1. In a particular non-limiting embodiment, the **TBDPS** protecting groups at positions C12 and C18 of compound 28 are removed by treatment with TBAF in THF; the triple bond at positions 6-7 of compound 28 is reduced by treatment with activated Zn; and the protected hydroxyl group at position C5 of compound 29 is deacetylated by treatment with NaOH.

[0011] Compound 28 used in the synthesis of RvE1 may be obtained, e.g., as depicted in **Scheme 2**, by reaction of compound 17 with compound 22, or by reaction of compound 16 with compound 23.

CLAIMS

1. A method for the synthesis of Resolvin E1 (RvE1) of the formula 30 starting from compounds 72 and 61, wherein PG each independently is a hydroxyl-protecting group, said method is carried out as depicted in Scheme 15 and comprises: (i) Wittig reaction of compound 72 with compound 61 in the presence of a strong base; (ii) removal of the hydroxyl-protecting groups with a deprotecting reagent to obtain compound 73; and (iii) hydrolysis of the ester group of compound 73, to obtain RvE1



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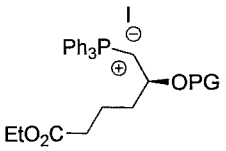

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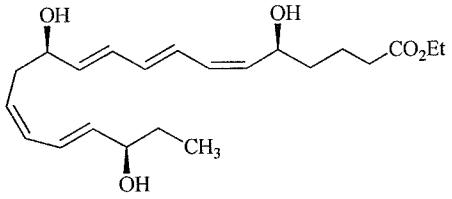

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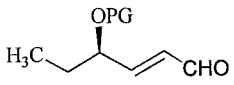
2. The method of claim 1, wherein said compound 72 is synthesized as depicted in Scheme 16 by (i) Wittig reaction of compound 54 and compound 70, wherein PG each independently is a hydroxyl-protecting group, in the presence of a strong base to obtain compound 71; and (ii) removal of the amide group of compound 71 with a strong base to obtain compound 72



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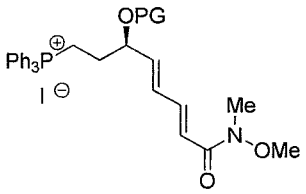

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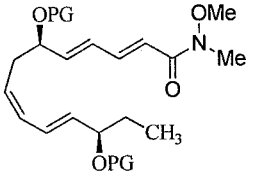

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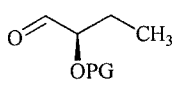
3. The method of claim 2, wherein said compound 54 is synthesized as depicted in Scheme 17 by Wittig reaction of compound 53, wherein PG is a hydroxyl-protecting group, and Ph_3P=CHCHO



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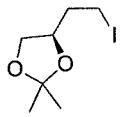
4. The method of claim 2, wherein said compound 70 is synthesized starting from compound 64, said method is carried out as depicted in Scheme 18 and comprises: (i) deprotection of the diol in the presence of a weak acid; (ii) protection of the hydroxyl groups to obtain compound 65, wherein PG each independently is a hydroxyl-protecting

group; (iii) Dess-Martin oxidation of compound 65 with Dess-Martin periodinate to obatin aldehyde 68; (iv) double Wittig reaction of aldehyde 68 with Ph_3P=CHCHO and then with Ph_3P=CHCON(OMe)Me to obtain compound 69; and (v) conversion of said compound 69 to the triphenylphosphonium salt 70 with triphenylphosphine



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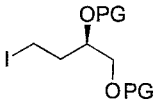

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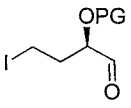

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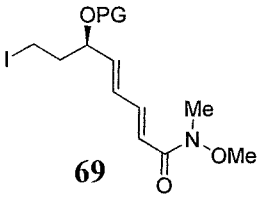

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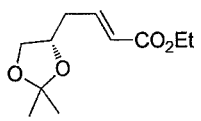
5. The method of any one of claims 1 to 4, wherein said hydroxyl-protecting group is *tert*-butyldimethylsilyl ether (TBDMS) or *tert*-butyldiphenylsilyl ether (TBDPS).

6. The method of claim 1, wherein said compound 61 is synthesized starting from compound 56, said method is carried out as depicted in Scheme 19 and comprises: (i) reduction and deprotection of compound 56, followed by tosylation and then iodination to obtain compound 59; and (ii) hydroxyl-protection of compound 59 followed by conversion to the triphenylphosphonium salt 61 with triphenylphosphine



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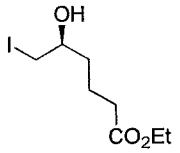

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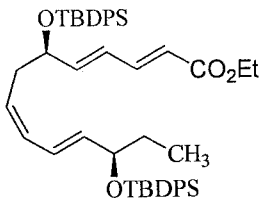
7. A method for the synthesis of Resolvin E1 (RvE1) of the formula 30 starting from compound 42, said method is carried out as depicted in Scheme 9 and comprises: (i) reduction of the ester group of compound 42 to obtain compound 48; (ii) Wittig reaction of compound 48 with compound 47 in the presence of a strong base to obtain an intermediate product: and (iii) removal of the hydroxyl-protecting groups at positions C12 and C18 of said intermediate product and deacetylation of the protected hydroxyl group at position C5 of said intermediate product, to obtain RvE1



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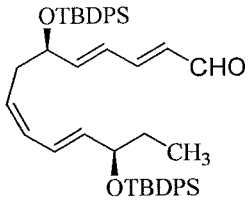

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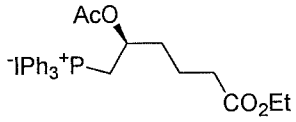

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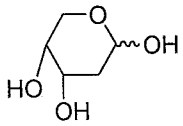
8. The method of claim 7, wherein compound 47 used in the synthesis is synthesized starting from 2-deoxy D-ribose (compound 34) as depicted in Scheme 10



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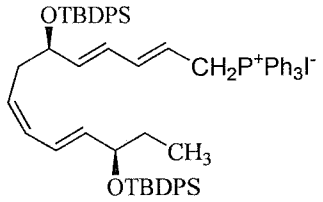
9. A method for the synthesis of Resolvin E1 (RvE1) of the formula 30 starting from compounds 43 and 46, said method is carried out as depicted in Scheme 11 and comprises: (i) Wittig reaction of compound 43 with compound 46 in the presence of a strong base to obtain an intermediate product; and (ii) removal of the hydroxyl-protecting groups at

positions C12 and C18 of said intermediate product and deacetylation of the protected hydroxyl group at position C5 of said intermediate product, to obtain RvE1



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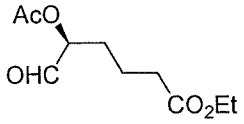

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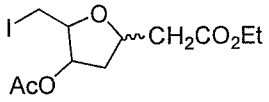
10. The method of claim 9, wherein said compound 43 is synthesized starting from compounds 37 and 38 as depicted in Scheme 12



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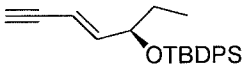

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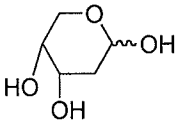
11. The method of claim 9, wherein said compound 46 is synthesized starting from 2-deoxy D-ribose (compound 34) as depicted in Scheme 10



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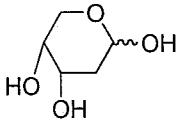
12. The method of claim 10, wherein said compound 37 is synthesized starting from 2-deoxy D-ribose (compound 34) as depicted in Scheme 13



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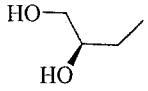
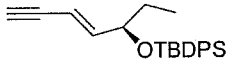
13. The method of claim 10, wherein said compound 38 is synthesized starting from compound 1 as depicted in Scheme 14



1 .

14. A compound selected from the herein identified compounds 38, 39, 40, 41, 42, 47, 59, 61, 65, 68, 69, 70, 71, 72 and 73



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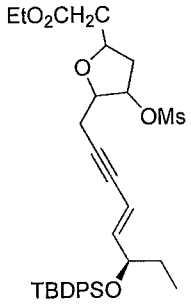

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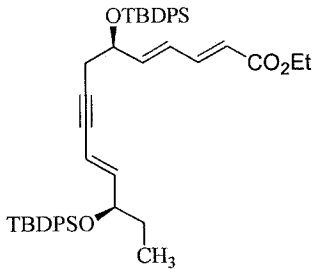

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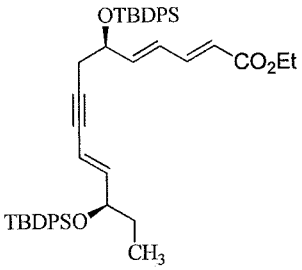

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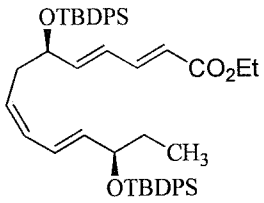

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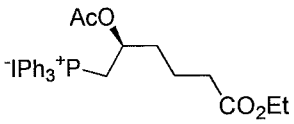

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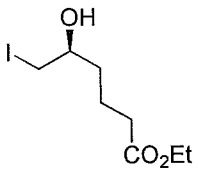

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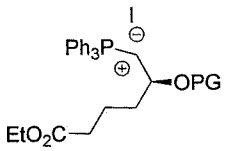

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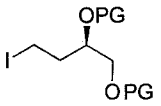

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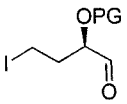

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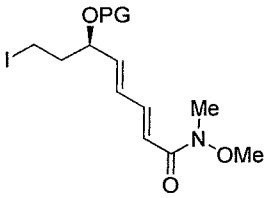

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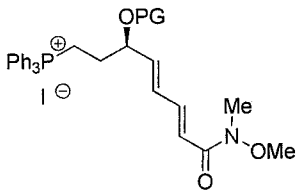

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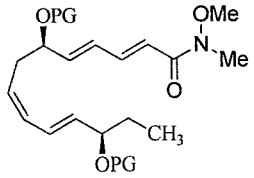

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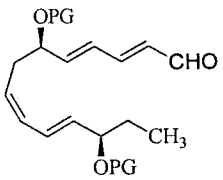

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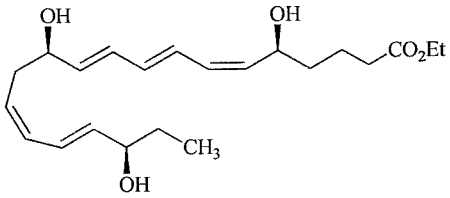

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